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RECENT ADVANCES IN THE PHYSIOLOGY OF REPRODUCTION IN RELATION TO THE ZONDEK-ASCHHEIM TEST FOR THE EARLY DETECTION OF PREGNANCY*

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The earliest significant contribution to the problem of reproduction was the description of the uterine tubes and ovaries, by Fallopius (1) in 1584. He stated that the ovarian cavities were filled with a fluid and sometimes with yellow solids. The next step of importance was that of De Graaf (2) who, in 1672, described the follicles bearing his name and referred to the yellow solids as "Conglomerated Glandular Bodies." Malpighi (3), in 1689, described these bodies in detail and proposed the name corpora lutea. De Graaf (2) maintained with the others who preceded him, that the presence of corpus luteum in an ovary was a positive evidence, either of a previous pregnancy or coitus. This finding was used in the Medicolegal practice, until Bischoff (4), in 1842, contradicted this dictum by showing the presence of corpus luteum during the menstrual period of virgins. This finding was verified by Corner (5) only as recently as 1915. Bischoff (4) was of the opinion that the ovaries were responsible for menstruation and pointed out a relationship between changes in the graafian follicles and changes in the menstrual cycle. This belief was elaborated by Pflüger (6), in 1865, who suggested that the menstrual flow was reflexively produced by the pressure of the enlarged graafian follicles on the ovarian nerves of the ovary. The relationship of ovulation and menstruation was subsequently the subject of considerable study by many physicians (7, 8, 9) including Aveling (10) who, in 1874, concluded from clinical observation and necropsy studies that there is a periodic development of the decidua for the reception of the fertilized ova. In failure of conception, degeneration of the decidua occurs and by uterine contraction it is expelled and determined as menstruation. The opinions of these investigators were summarized by Power's (11) famous dictum, "Women menstruate because they do not conceive."

Mary Putnam Jacobi (12), in 1878, carried out studies which indicated that there is a "rhythmic wave of nutrition," which rises and falls

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at each monthly period. She observed an increase of urea excretion a few days preceding and a decrease during and after menstruation; also a rise in temperature before, and a decrease during and after. She believed this indicated that the process of menstruation was under a central control. Goodman (13), in 1878, followed with his cyclical theory of menstruation and Stephenson (14), in 1882, with his so-called wave theory. Pflüger's neurogenic theory of menstruation was enthusiastically accepted until Leopold (15), in 1883, and Leopold and Mironoff (16), in 1894, found in surgically treated cases that ripened graafian follicles were present in the absence of menstruation. They made the further observation that typical and atypical corpora lutea were present in cases with both regular and irregular menses. This suggested that menstruation and ovulation were not synchronous, but could occur independently of each other.

Knauer (17), in 1894, demonstrated for the first time that the ovaries mediated their influence in menstruation and pregnancy through an internal secretion. He transplanted ovaries in animals from the normal site to the abdomen and showed that the normal influence was maintained to the extent of pregnacy. Frank (18), in 1898, demonstrated the same in human beings. While resecting the adnexa of a patient he transplanted a piece of healthy ovary into the stump, and pregnancies occurred on two subsequent occasions. In 1902, Morris (19) transplanted an ovary from one woman into the uterus of another whose ovaries were atrophied. Four years later pregnancy and delivery occurred. Similar experiences have been reported by others (20 to 28).

In 1900, Knauer (29) and Halban (30, 31), independently, offered the suggestion, that the ovaries give off a chemical substance which circulates in the blood and influences the endometrium in the production of menstruation. Halban (32) stated that menstruation is established only when the follicles in the ovaries remain active. The ovaries were said to be not only indispensable for their physiological effect on menstruation, but also to have a trophic influence on the genitalia. It had been shown that when a new born animal is castrated the genitalia atrophy. It was Frankel (33), however, who in 1903 was able to prove that menstruation in the human being is brought about through the influence of corpus luteum secretion. In 1910, for the first time, he (34) offered experimental evidence that corpora lutea possessed the function to elaborate a hormone for the progestational proliferation of the endometrium and for the maintenance of its nutrition during the early stages of pregnancy. He castrated a pregnant rabbit during the first weeks of gestation and showed that such animals regularly aborted. Knaus (35, 36) corroborated this by demonstrating that with subcutaneous injections of corpus luteum, pregnancy could be prolonged in rats from one to six days. Hisaw (37) produced relaxation of the pelvic ligaments in the guinea pig with mobilization of the pelvic bones with the same hormone.

Many investigators have experimentally proven that the absence of estrus is due to the persistence of corpora lutea. If they are removed or

destroyed estrus will recur within three to eight days and the animal can again breed. Meyer (38, 39), Ruge (40), Schroeoder (41 to 45), Halban (46) and Novak (47) pointed out that the cyclical changes of the endometrium are dependent on the corpora lutea (figure 1). If fertilization

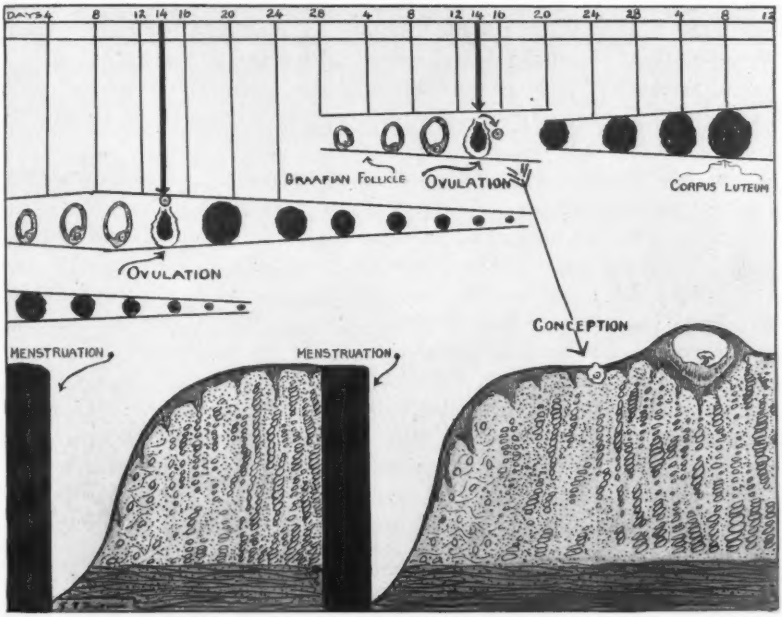


Fig. 1. A schematic diagram representing the correlation of the development of the corpus luteum and the endometrium during a menstrual cycle and in pregnancy. In menstruation the corpus luteum involutes, whereas in conception it grows larger continuing its hormonic influence on the endometrium, resulting in the formation of the decidua. (Modified from Schroeder, R.).

takes place the corpora lutea persist unchanged; if not they undergo degenerative changes and menstruation occurs. Loeb (48, 49) maintained that the presence of corpus luteum hormone inhibits ovulation during pregnancy, that when it becomes much diminished menstruation occurs. This opinion was corroborated by Beard (50), Frankel (33) and Dixon and Marshall (51), who hold also that the inception of labor is dependent upon this decrease in corpus luteum secretion. Long and Evans (52) have shown by histological studies that the changes occurring in the corpus luteum of rats shortly before parturition is indicative of cessation of function and they suggest the possibility of postponing parturition in human beings by the administration of corpora lutea.

Thus far the contributions demonstrating that a hormone from the ovary, probably the corpus luteum, is responsible for the menstrual cycle and the changes in the decidua, preliminary to pregnancy were outlined.

The relationship of this hormone to clinical amenorrhea and menopause was still an unsolved problem. In 1915, Tuffier (28) was able to re-establish menstruation in a woman with amenorrhea of two years' duration and another with menopause, by injecting 24 cc. of defibrinated blood obtained from a patient a day before menstruation. Corner and Allen (53) castrated rabbits a day after mating; when daily injections of corpora lutea extract, from 0.1 to 0.5 cc., were made the animals maintained their normal state of pregnancy to full term. Engle and Mermod (56) found that transplanting fresh anterior pituitary into pregnant rats and mice in the early stages of gestation prevented implantation and led to resorption or expulsion of the fetus.

In 1917, Stockard and Papanicolaou (57) proposed a method whereby a microscopic examination of smears of the vaginal epithelium of living guinea pigs could be used as an index of the ovarian activity in the estrus cycle. The discovery was later elaborated by Long and Evans (58) on rats, and by Edgar Allen (59) on mice. On this basis Allen and Doisy (60) devised a test whereby the quantitative activity of ovarian and placenta extracts could be determined. They were able to classify the estrus cycle into four distinct stages: Diestrus, quiescent stage, characterized by the presence of but a few leucocytes, epithelial and mucous cells; Proestrus, the proliferation stage, in which a great number of nucleated squamous cells are present; Estrus, sexual excitement stage, in which great numbers of squamous cells, some nucleated and non-nucleated epithelial cells are present; Metestrus, the building up stage, and here leucocytes, epithelial and mucous cells are present. This simplified method stimulated investigators to further research in this field. Zondek and Aschheim (61) used this method to show that ovarian hormone was excreted in urine. When such urine is diluted and further injected into animals the characteristic vaginal changes are produced. By determining minimal dilution changes, a quantitative index of ovarian hormone can thus be obtained in terms of mouse units. A unit represents the smallest amount of a liter of urine in cubic centimeters which is capable of producing estrus in an infantile or adult castrated mouse. Frank and Goldberger (62) and others (63 to 65) using this method found the hormone to be present in the blood of a guinea pig in estrus, and reported the highest yield just before menstruation. They (66) also demonstrated a considerable amount in the menstrual discharge. With the same method they showed this hormone to be present in the blood of pregnant women. Loewe and Lange (64) found it in human urine. Iscovesco (67) found it in placental tissue. The same hormone has been demonstrated in small quantities in corpora lutea (68, 69), folliculin (60, 70), plants (67), yeast (71, 72), feces (73), bile (74) and a large amount in amniotic fluid (75). In 1930, Doisy (76) and his co-workers in this country, and Butenandt (77) in Germany, independently, isolated a crystalline substance from the urine of pregnant women and demonstrated this to be chemically identical with folliculin (ovarian hormone)

except that it is of a considerable higher potency. Doisy (76) proposed the name "Theelin" for this hormone a name derived from the Greek word, "Theelus," signifying "female." Collip (78) isolated two hormonal fractions from human placental tissue and regarded the placenta as a reservoir for this hormone. It seems probable that this organ is responsible for the marked increase in the production of folliculin during pregnacy, since it has been shown that the removal of both ovaries in pregnancy does not diminish the amount of folliculin in the blood and urine.

Courrier and Potvin (79) in 1926, injected folliculin into castrated female rabbits and obtained growth and congestion of the uterus, a condition which had been attributed for many years to corpus luteum. Folliculin seems to prepare the uterus so that it can respond to the hormone of the corpus luteum. The latter appears to function only in the presence of the folliculin. In accordance with the observation of Adler (80), Papanicolaou (81) also Parkes (82), who are of the opinion that folliculin and the corpus luteum hormone are antagonistic to each other and that during pregnancy the corpus luteum is in ascendancy until parturition. Parkes and Bellerby (83) have demonstrated that by injecting folliculin in white mice they were able to prevent conception or terminate pregnancy. Margaret Smith (84), however, found that by injecting a similar ovarian follicular extract in white rats, she could interrupt pregnancy only up to the fifth day and not thereafter. Similar experiences by others (85 to 90), who showed that although corpora lutea and folliculin hormones are required for the maintenance of pregnancy, yet, an excess of either during pregnancy will cause abortion, thus proving there must be a ratio or balance of hormone content. Kelly (91) has reported that the injection of pregnancy urine into pregnant guinea pigs invariably produces abortion. Doisy (92) and his co-workers prolonged the gestation period by administering Theelin to pregnant rats in the latter half of pregnancy and found on necropsy that the fetus was usually dead, fully developed, often of greater than normal size and partially resorbed.

Hermann and Stein (93) reported the attainment of sex maturity in young rats and rabbits by injecting ovarian hormone. They also observed degenerative changes in the testes in adult rats and rabbits by prolonged injections of large quantities of corpus luteum hormone, which were similar to those produced by x-ray, as reported by Parkes and Bellerby (83) and Geller (94). They have also proven that x-ray exposure on the head inhibits the action of the anterior pituitary body, causing sterility due to degenerative changes of the follicles in the ovaries. A number of investigators (95 to 97) have produced premature puberty in animals by placental and ovarian hormones. Marshall (98) has demonstrated that by removing the ovaries from immature animals, a cessation of development is caused in primary sex organs and secondary sex characters. Steinach (99) has shown that the ovarian interstitial cells are responsible for the internal secretion maintaining the normal nutrition of the uterus, and rep-

resent the puberty glands responsible for the sex characters. A castrated male with transplanted ovaries becomes feminized; and, likewise, a female with transplanted testes develops masculinity. Voronoff (100) claimed to be able to rejuvenate the aged by testicular transplanting.

Zondek and Aschheim (61, 101 to 104) and independently Smith (105 to 109) began a series of studies which showed that the hormone of the anterior lobe of the pituitary body was normally excreted in the urine in pregnancy and that such urine was capable of producing estrus. Feeding, implanting and injecting infantile mice with anterior lobe of the pituitary gland resulted in advanced morphological and functional changes in the ovaries and menstruation occurred approximately 100 hours later. These same changes were regularly produced after the injection of the urine of pregnant women into mice. This finding is the basis of the test which Zondek and Aschheim proposed for the diagnosis of pregnancy. They have shown that other conditions, such as carcinoma of the cervix of the uterus, hydatidiform mole and chorionepithelioma increase the formation of anterior pituitary hormone.

Aschheim (110) is of the opinion that in normal pregnancy the anterior pituitary body secretes a hormone of importance in the growth of the fetus. Since there is no fetus in hydatidiform mole the excess of this hormone exerts its influence upon the ovary. Rössler (111) in a study of thirteen cases of hydatidiform mole and chorionepithelioma determined that the increase may be as much as three-fold in the non-malignant types and as much as eight to fifteen times the normal in the malignant variety. Ehrhardt (112), Schultz-Rhonhof (113), Fahlbusch (114), Fels (115), Otto (116) and others (117 to 119) report a group of cases in which the Zondek-Aschheim test for pituitary hormone was found to be of great diagnostic and prognostic value.

The changes in the anterior pituitary glands in pregnancy have been studied by Erdheim and Strumme (120). They observed an enlargement of the anterior pituitary body in the latter months of pregnancy of such magnitude as to produce a bilateral hemianopsia from pressure on the optic chiasm. The pronounced coarseness and enlargement of the features (general acromegaly) in the late months of pregnancy is probably of pituitary origin. Cushing (121) has described similar changes in the anterior pituitary lobe of the pregnant bitch, cat and rabbit. Wagner (122) was the first to report a case of a tumor in the anterior pituitary gland associated with tremendous luteinization of both ovaries. The opinion has been expressed that the changes produced in the anterior pituitary body in pregnancy are due to the presence of foreign protein. Berblinger (123), Adachi (124), Lehmann (125) and Baneicki (126) have shown that the placental substance and ovarian hormone when injected into animals cause histological changes in the anterior pituitary gland similar to those in pregnancy. Berblinger (123) and Bieble and Knaus (127) were also able to produce changes in these glands like those in pregnancy by injections

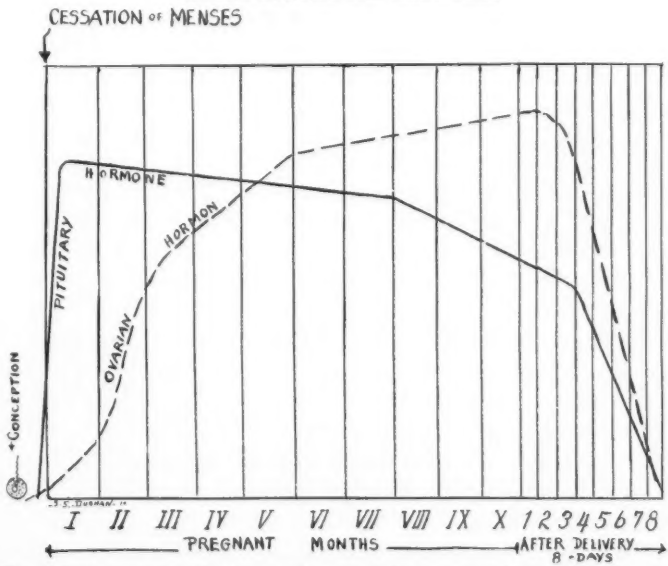
of peptone. Baneicki (126) made similar observations after the injection of pregnant urine or horse serum.

Zondek and Aschheim (128) regard the anterior pituitary gland as the motor of ovarian function. Smith's (129) studies showed that menstruation failed to occur after hypophysectomy. The anterior pituitary hormone stimulates the ovaries with the production of both folliculin and corpora lutea hormones. Long continued amenorrhea in a patient is then theoretically due to either an insufficient production of anterior pituitary hormone or cessation of ovarian function. In women, when periods occur more frequently than usual, it is reasonable to assume that an increased amount of ovarian hormones are being secreted. This may be due to an excessive amount of pituitary stimulation. Steinach and Kun (130) were able to reactivate senile ovaries by anterior pituitary lobe transplantations. Teel (55) and Evans and Simpson (131) demonstrated that by injecting fresh anterior pituitary glands, gestation is prolonged for several days past the normal period. They suggest that this fact may account for still births.

Zondek and Aschheim (128) pointed out that the blood and urine of pregnant women shows a marked increase of both pituitary and ovarian hormones (chart 1). With the onset of pregnancy the rise of the ovarian

CHART I

CURVES ILLUSTRATING CONCENTRATION OF PITUITARY AND OVARIAN HORMONES DURING PREGNANCY
AFTER ZONDEK AND ASCHHEIM



The ordinates of this chart are not expressed but the values indicated are based on actual measurements of anterior pituitary and ovarian hormones in the urine. The unit for this measurement is the smallest part in ccm. of a liter of urine which is capable of producing estrus in an infantile adult castrated mouse.

hormone is gradual over a period of weeks. In contrast, the pituitary hormone rises acutely, a high level being reached a few days after conception. This remains high until the end of the eighth month of pregnancy, after which it gradually drops, reaching normal the eighth day after delivery. The abrupt increase of the pituitary hormone makes possible the recognition of pregnancy as early as five days after the expected period. In the first eight weeks of pregnancy, Zondek and Aschheim (104) were able to extract 300 to 600 mouse units of folliculin from a liter of urine and 5,000 to 6,000 mouse units of folliculin and only 2,000 to 3,000 mouse units of anterior pituitary hormone. The urine of pregnant women is being used as the source for commercial ovarian and anterior pituitary hormone preparations.

The action of the pituitary hormone on the ovaries is in contrast to the action of folliculin (ovarian hormone). Long and Evans (58, 132) and Allen (59) have shown that the latter produces changes confined to the uterine glands and vagina, the structures of the ovaries being unaltered. The mere occurrence of ovarian hormone in the urine is not diagnostic of pregnancy for this is occasionally found in functional disturbances of the ovarian gland, such as may occur at menopause, in certain amenorrheas, hyperthyroidism and myxedema.

Zondek and Aschheim (133) have demonstrated that the anterior pituitary body liberates three distinct hormones, for growth, for ovulation and for luteinization. The latter two hormones have been termed by Zondek (134) as Prolan A and B, and they are commercially prepared as such. He suggested the possibility of a fourth hormone for metabolism. Prolan A, the ovulation hormone, develops the graafian follicles in the ovary. The hormone of the folliculin fluid stimulates the uterus to grow and proliferation of the basal layer of the endometrium. Prolan B, the luteinization hormone, luteinizes the cells of the ruptured follicles and causes the formation of the second ovarian corpus luteum hormone. This acts on the endometrium, producing characteristic changes of the premenstrual phase by the progestational proliferation of the endometrium (figure 2). Zondek (135) isolated large amounts of Prolan A (ovulation hormone) from the urine of patients in early menopause and after castration.

The average test requires the use of four or five infantile mice, three to four weeks old, weighing approximately six to eight grams. Mice weighing less than six grams frequently die before the completion of the test. Mice start the estrus cycle normally about the sixth week. The patient's morning urine is chosen because of its greater concentration. It is important that it should be collected in a perfectly clean utensil, in as much as antiseptic drugs, especially perfume, destroy the hormone. When examination is to be delayed, however, one drop of cresol may be added to each ounce of urine as a preservative. Alkaline or neutral urine should be acidified, sediment filtered out if present, and the urine kept in a cool place

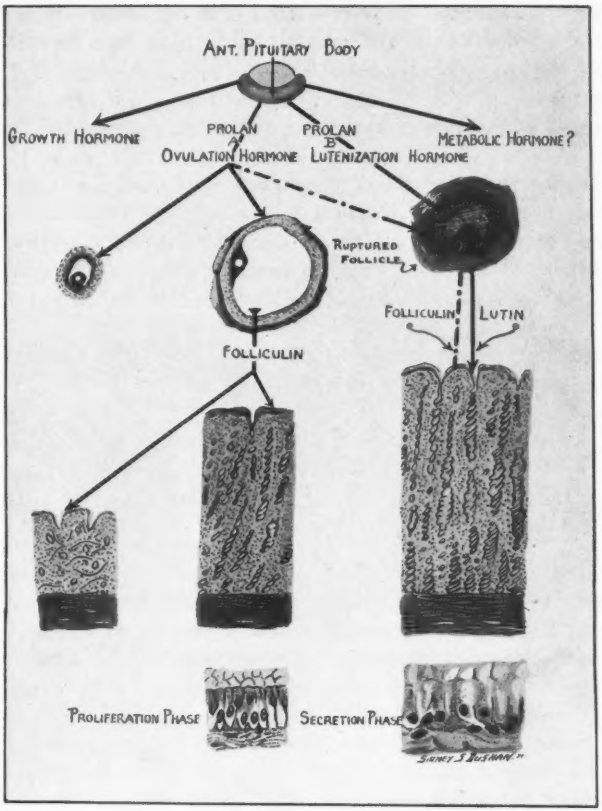


Fig. 2. The above diagram by Zondek indicates interrelation of the hormones at play and in the physiology of menstruation, conception and pregnancy. Prolan A & B is liberated from the anterior pituitary body. Prolan A (ovulation hormone) stimulates the maturation of the graafian follicles with the production of folliculin, which further develops the basal layer of the endometrium. Prolan B (lutenization hormone) stimulates the production of corpus luteal hormone which in turn develops the endometrium further.

until used. The dose injected is conveniently recorded on each mouse by marking with India ink or picric acid. The urine is injected subcutaneously 0.2 to 0.4 cc., six times within the first 48 hours: two injections the first day, with a five-hour interval, three injections the second day, with intervals of three and five hours, respectively; and one injection on the third day on the 48th hour.

The mice are killed approximately 96 to 100 hours after the first injection. This may be done with illuminating gas, ether or chloroform. Ethyl-chloride has been more satisfactory in my experience. Only a small quantity is required and very little odor is produced.

Zondek (133) has recently improved on his so-called original 48-hour emergency test by concentrating the urine six times and making six injec-

tions of 0.4 cc., at three-hour intervals the first and second days. The animals are necropsied on the 51st or 57th hour. This may be reliable for a negative as well as a positive result.

Criterion of a Positive Test: A positive test is indicated by observing gross changes in the ovaries and these have been grouped by Zondek and Aschheim (102 to 104) as reactions II and III. Reaction I, in itself, is not reliable for the diagnosis of pregnancy as it concerns changes in the uterus and vagina alone. Reaction II concerns the formation of the so-called blood points on the surface of the enlarged ovary. These are discretely distributed, brownish purplish areas the size of a common pin head, and are the gross representation of hemorrhage into the enlarged graafian follicles. Reaction III concerns the detection of the corpora lutea which appear discretely on the surface of the ovary, as yellowish pin head sized areas. The presence of either reaction (II or III) in one ovary is positive of pregnancy.

Zondek and Aschheim as well as other investigators have reported an accuracy of 98 to 100 per cent with this test. The author has applied the test in the study of 370* patients in private practice, with but five failures (Tables I, II and III). The sources of error in each of these five cases was determined (136).

TABLE 1

Provisional—Diagnoses	Number of Cases	Reactions	
		Negative	Positive
1. Pregnancy	138	43	95
2. Functional Amenorrhea	71	52	19
3. Metrorrhagia	54	39	15
4. Menopause	49	36	13
5. Normal	15	14	1
6. Fibromata Uteri	21	16	5
7. Salpingitis	9	7	2
8. Miscarriage	5	4	1
9. Tubal Pregnancy	3	0	3
10. Ovarian Cyst	5	5	0
Total	370	216	154

TABLE 2

Final—Diagnoses	Number of Cases	Reactions	
		Negative	Positive
1. Pregnancy	150	0	150
2. Funtional Amenorrhea	67	67	0
3. Metrorrhagia	47	47	0
4. Menopause	53	53	0
5. Normal	14	14	0
6. Fibromata	19	19	0
7. Salpingitis	7	7	0
8. Miscarriage	5	4	1
9. Tubal Pregnancy	3	0	3
10. Ovarian Cyst	5	5	0
Total	370	316	154

*Since the reading of the paper in June, 1931, we have performed 240 additional test examinations.

TABLE 3

Period of Pregnancy	Number of Cases	Reactions	
		Negative	Positive
4–7 days after the expected period	33	2	31
7–10 days after the expected period	55	2	53
2–4 weeks after the expected period	44	1	43
1–3 months after the expected period	19	0	19
3–7½ months after the expected period	2	0	2
Total	153	5	148

Freidman (140) has recently employed the rabbit as the animal of choice as it has the advantage of an early determination. Rabbits ovulate only after copulation as pointed out by Heape (137) and verified by Ancel and Bouin (138) and Hammond and Marshall (139). The technique suggested by Freidman is six injections of urine of 4 cc. each, thrice daily, into the vein on the margin of the ear. The animal is autopsied on the 48th hour after the first injection and the ovaries are viewed for the presence of corpora lutea or corpora hemorrhagica (Figure 3). Although Freidman (141) has pointed out that a single injection of 5 cc. of pregnant urine may provoke ovulation in rabbits, he did not regard one injection reliable for a negative test. Schneider (142), however, found the single injection satisfactory in 100 cases. The rabbits received 5 to 7 cc. of urine and were autopsied 24 to 30 hours later.

We have applied the rabbit test in 40 cases, with the single injection method, using 10 to 15 cc. of urine generally concentrated from amounts varying from 60 to 150 cc. Only two failures were noted. In one the specimen was apparently not sufficiently concentrated for the test; in the second, the rabbit used was apparently too young, which bears out Schneider's findings that rabbits under three months of age are not reliable. Mice were used in every instance as a control.

Recent investigations in the realm of the internal secretions of the anterior pituitary and the ovarian glands mark a monumental advance in our knowledge of the physiology of reproduction, and will serve as a solid basis for future research.

CONCLUSIONS

A review of the recent advances in the physiology of menstruation and pregnancy has led to the following conclusions:

1. Folliculin plays an important role in the building up of the basal layer of the uterine endometrium in the first stage of menstruation. The presence of the corpus luteal hormone is responsible for further development of this endometrium, and as a result, a diminution of the same hormone, desquamation and extravasation of the endometrium occurs.

2. The persistence of the action of the corpus luteal hormone results in the development of the endometrium into the decidua and in the first months is indispensable to pregnancy. The termination of parturition is probably brought about by a diminution or disappearance of the corpus

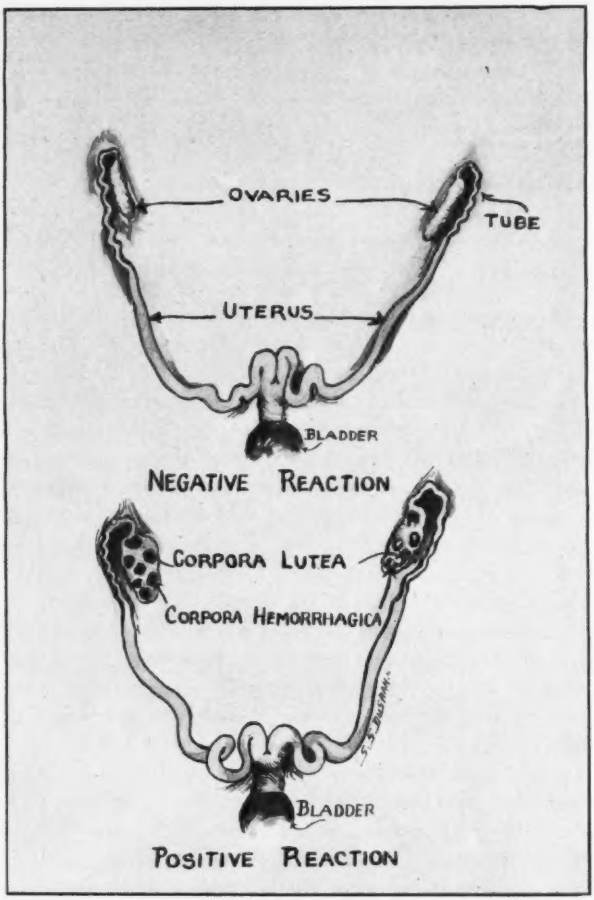


Fig. 3. The above diagram represents a negative and a positive Zondek-Aschheim reaction in rabbits' ovaries forty-eight hours after the injection of urine. (Modified from Schneider.)

luteal hormone. An increase of this hormone in the late months results in prolongation of pregnancy.

3. The hormone of the anterior pituitary body is increased in the blood and urine in pregnancy and acts as a stimulus for the production of the corpus luteum. The excretion of this pituitary hormone in the urine, and for this reason the capacity of such urine when injected into rodents to produce characteristic changes in the ovaries, has led to a simple and reliable test for pregnancy.

SUMMARY

The historical development of contributions relating to recent advances in the physiology of reproduction is reviewed and the basis of the Zondek-

Aschheim test for the early diagnosis of pregnancy presented. This test was applied with excellent results in 370 cases and these are tabulated. A brief outline of technique is given.

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FUNCTIONAL RELATIONS OF THE HYPOPHYSIS AND THE BRAIN*

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The pituitary body and the brain long have been considered as possessing associated functions. In earlier times the gland was described as having an action similar to that of a bilge pump, collecting the excrementous slime formed by the brain and passing it on to the nostrils. Most of us can remember when nearly all of the internally-secreting glands were described on the basis of their topographical relation to some entirely different organ or system. In a certain text-book of histology still occasionally used by medical students the pituitary body is described in the chapter on the brain, the thyroid gland is treated with the respiratory system, and the suprarenals with the genito-urinary organs. Although the development of endocrinology has caused these glands to be placed in an independent category, reasons still remain for considering the pituitary body and the brain together. In fact, it recently has become common to speak of the posterior pituitary and the adjacent region of the hypothalamus as constituting a "functional unit," or an "interacting mechanism."

Now general concepts are of value when they open new vistas of scientific vision and inspire further more precise and critical experiments. If a general concept gives an air of finality to a particular viewpoint, further experimentation is hindered; thus scientific progress is impeded. The object of this paper is to consider briefly the morphological and experimental basis for, and against, some of the present concepts of the functional unity of the hypophysis and the brain.

ANATOMY OF THE HYPOPHYSIS

As is well known, the pituitary body arises from two different sources. The neural portion develops from an evagination of the brain floor and forms the infundibulum, infundibular stalk and process, or neural lobe. The epithelial portion is derived from Rathke's pouch, an evagination of the lining of that part of the primitive mouth which later becomes the nasopharynx. This part comes into contact with the neural portion, later loses its connection with the oral epithelium, and finally differentiates into three distinct portions, pars anterior proprior, pars intermedia, and the less well known pars tuberalis (5).

The pars anterior proprior is not in direct contact with the neural portion, and on that account is called by Tilney (47) the "pars distalis." The

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pars intermedia and the pars tuberalis, on the other hand, become intimately related, the former with the neural lobe and stalk, and the latter with the infundibulum and adjacent tuber cinereum. Collectively, they are termed by Tilney the "pars juxta-neuralis."

The residual lumen of Rathke's pouch, when such persists, separates the anterior lobe proper from the pars intermedia and the neural lobe. The first constitutes the "anterior pituitary" and the last two together compose the physiological "posterior pituitary."

Attention has been called (7) to the fact that the pars tuberalis lies mainly above the diaphragma sellae, embedded in the pia mater of the infundibulum and tuber cinereum.

The adjacent floor of the hypothalamus, particularly that part extending from the optic chiasm to the mammillary bodies, contains certain groups of nerve cells, the importance of which has recently been established.

For much of our knowledge of the histology of these nuclei and of their location and relations we are indebted to the work of Malone (33, 34), Rioch (41) and Morgan (36). Chief among the cell-groups of this region are: the substantia grisea centralis, nucleus supraopticus, nucleus paraventricularis, nucleus mammillo-infundibularis, nucleus paramedianus and the subthalamic body. These are considered to be autonomic centers of the diencephalon partly on the basis of clinical and experimental data and partly because of the structural similarity of their nerve cells to known autonomic neurones.

PARS INTERMEDIA AND NEURAL LOBE

Even more intimate relationships, demonstrable only by histological methods, exist between the pituitary and the brain. Most intimate of all is the association of pars intermedia and neural lobe tissues. This is found, in varying degree, in all vertebrate classes. In the lower fishes (46) many hollow pouches of the neural lobe project into the pars intermedia. In higher fishes solid projections of neural lobe and pars intermedia interdigitate. Herring observed (27) that groups of cells and colloid material from the pars intermedia appear to push their way into the neural lobe toward the third ventricle. This was corroborated by Cushing and Goetsch (21) and forms the basis for the theory that the posterior lobe secretion enters the cerebro-spinal fluid.

Posterior pituitary preparations are commonly made by extracting the entire posterior lobe. However, the active substance may be obtained from either pars intermedia or neural lobe separately. It is believed to be elaborated in the former and to pass into the latter.

These facts at once raise the question as to whether the pars intermedia can function if separated from neural tissue. The nearest approach to an answer has been obtained by experiments on Amphibia. When the epithelial hypophysis is removed from a young amphibian larva the animal soon becomes silvery (1, 42). This condition the writer (6) showed could

be corrected by treatment with pars intermedia extracts but not with anterior lobe. This has been amply confirmed by Allen's (2, 4) transplantation experiments. Hogben and Winton (28) devised a delicate biological test for posterior lobe extracts utilizing the darkening effect of the substance on the adult frog. Fenn (24), by perfusion, greatly increased the delicacy of the method.

Blount (12) transplanted the hypophyseal region before invagination of the pituitary rudiment. He found that when the epithelial portion is transplanted alone it will not develop, but that if neural tissue is included in the transplant a functional gland is obtained. The writer (1931 experiments, as yet unpublished) has found that when the epithelial hypophysis is transplanted to a heterotopic position after it has invaginated the anterior lobe continues to differentiate and to function normally. This is shown by influence on growth and on thyroid and adrenal glands. The pars intermedia, however, as shown by pigmentary reactions, seems unable to develop and function unless it maintains connection with neural tissue. At a considerably later stage, when all lobes of the gland are well differentiated, Allen (2) has successfully transplanted pure pars intermedia tissue which functioned without being in relation to neural tissue. It seems, then, in so far as can be told by the pigmentary effects in these amphibian experiments, that the neural lobe is necessary for the early development and differentiation of the pars intermedia but that it is not required for proper functioning after the latter has become fully differentiated.

NERVE SUPPLY

The nerve supply of the pituitary is a matter of considerable interest. It is usually stated that its sympathetic nerves are derived from the carotid plexus (22).

That there may be a direct nerve supply which passes through the infundibulum and neural lobe is indicated by the work of several investigators. Greving (25, 26) traces large bundles of nerves from the nucleus supraopticus through the infundibular stalk to the posterior lobe of the pituitary. He states that this nucleus is the center for the regulation of hormone production in the posterior lobe.

Pines (37) and Croll (18) have described the nerves of the pituitary. The latter has studied their distribution in the neural lobe and the pars intermedia, but does not trace them from their ultimate source.

Kary (31) and Levy (32) observed degeneration in the cells of the tuberal nuclei following injuries to the posterior lobe of the pituitary. These degenerative changes are assumed to be in the nature of an axone-reaction but their occurrence as a possible result of interference with the blood supply is not excluded.

Maddox, in Cushing's laboratory (20), after applying a clip to the pituitary stalk, has studied the resulting secondary degeneration in the nerve fibers of the posterior lobe.

All these observations indicate the probability of nervous connections between the diencephalic nuclei and the posterior lobe. If any of these fibers pass to the pars intermedia anatomists face the disturbing necessity of naming and numbering a new cranial nerve!

VASCULAR RELATIONS

Equally novel are some of the recent observations concerning the vascular drainage of the pituitary body. Popa and Fielding (38, 39) have observed in the stalk of the human pituitary a system of vessels arranged after the manner of a portal system, which they call the "hypophyseoportal veins." In the words of these investigators:

> "Inferiorly, these vessels collect blood from the pars anterior, pars intermedia, pars tuberalis and pars posterior of the pituitary. Then they ascend in the stalk as parallel veins, which after a short course acquire thick neuroglia sheaths. Sometimes one glial sleeve contains several such vessels. There is no surrounding capillary net served by the vessels while they are thus ensheathed and the tissues of the stalk between the glial cylinders appear to be without blood vessels of any sort.
>
> "Superiorly, beneath the infundibular recess of the third ventricle, these vessels of the portal system lose their heavy neuroglial wrapping and open out into a network of very fine channels. This may be called the secondary distributing net."

The secondary net is not haphazard in its distribution in the hypothalamic region but seems to have definite connection with certain nuclear groups. Further, "colloid material is found in association with the vessels of this portal system. Sometimes it is found within the vessels and sometimes in the perivascular sleeves. It can also be detected among the cells of certain hypothalamic nuclei." In the matter of colloid distribution in the hypothalamus the observations of Popa and Fielding are confirmatory of those of Remy Collin (17).

These portal vessels are found in various stages of contraction or expansion, suggesting that they are part of a mechanism for regulating the amount of colloid, or other secretion, carried to the hypothalamus.

FUNCTIONS OF PARTS OF HYPOPHYSIS

With these various morphological observations in mind, what can reasonably be accepted as the normal function of the parts of the pituitary and brain concerned and to what extent can these be shown definitely to constitute an "interacting mechanism"?

First, what are the known normal functions of the pars intermedia, pars neuralis and pars tuberalis of the pituitary?

Very little is known of the normal physiology of the pars intermedia. Most of what is commonly stated as its normal function is based upon the pharmacological effects of its extracts. Whether, for example, it normally exerts an influence upon smooth muscle of uterus or blood vessels or upon water metabolism or excretion is for the most part entirely unknown.

Whether the colloid material which is held to pass from the pars intermedia into the neural tissue is truly the active secretion of the part is likewise quite unproven.

Only the pigmentary control seen in amphibia has been proven to be a definite function of the pars intermedia by all the tests required to demonstrate hormonal action. There was shown first the pigmentary reversal when the pars intermedia atrophies or is removed, and secondly, the restoration of normal color when this lobe alone is grafted or its extracts administered. The application of this observation to human economy is not yet apparent.

The function of the neural lobe likewise is obscure. Does it manufacture a secretion itself or does it receive its active ingredients from the investing pars intermedia and subject these to maturing or other processes? Personally, the writer is inclined to the latter view. Allen (3) holds that the pars nervosa may exert a specific influence upon the distention of the body wall in amphibia.

As regards the normal function of the pars tuberalis little has been even conjectured. On comparing the effects of extracts prepared from the different parts of the ox pituitary Atwell and Marinus (10) found that extracts of the pars tuberalis exerted only about one-seventh as great oxytocic or pressor effect as extracts of the pars intermedia. We ascribed such small action as was obtained to contamination from neural stalk tissue, since it was not possible to free the pars tuberalis entirely from the latter. Marinus later (35) attempted to compare the growth effects of pars tuberalis and pars anterior by feeding experiments in rats. Although the method of feeding is open to serious objection, Marinus claimed to have obtained definite growth effects with anterior lobe but not with pars tuberalis. This was later definitely proven by the writer (9) by means of parenteral injections of pituitary suspensions into hypophysectomized frog tadpoles.

These observations, though largely negative, serve to show that the pars tuberalis is different from the other parts of the pituitary. The effect of pars tuberalis extract on urine secretion will be referred to later.

HYPOPHYSIS AND BRAIN

Secondly, what is it reasonable to believe concerning the influence of the hypophysis upon the adjacent parts of the brain? Do the secretory products of the pars intermedia or of the pars tuberalis, or of both, pass through the tissue spaces of the neural stalk to reach the hypothalamic nuclei or to enter the cerebro-spinal fluid? Or are these secretory products carried to the brain floor by special veins such as the hypophyseal portal system described by Popa and Fielding? It certainly is not reasonable to believe that all of these possibilities actually exist side by side. Furthermore, the existence of any one of them places limitations on the concept of hormone production by these parts of the gland. Commonly hormones do not exert their effects on adjacent tissues exclusively or even principally. Neither is it necessary that they be transported by special subdivisions of the vascular system.

Is it not at least equally reasonable to believe that the products of these lobes pass into the general circulation and that they may act selectively upon the nuclei of the hypothalamus?

Undoubtedly some of these questions could be answered by the successful grafting of the separate lobes into hypophysectomized mammals.

Also what is it reasonable to believe concerning the influence of the hypothalamic nuclei on the pituitary body? Do the nerve fibers which have been seen to pass from these nuclei to the neural lobe of the hypophysis actually pass on to the pars intermedia and terminate there in secretory endings? A definite answer cannot be given until further morphological and adequate physiological studies have been made. The willingness to accept these possibilties as actually existing, in the absence of adequate proof, shows again, in the writer's opinion, a confusion of propinquity of position with functional association. Again, is it not equally reasonable to believe that the hypothalamic nuclei, as autonomic centers of the brain, may influence the pituitary, as they probably do other endocrine glands, through the sympathetic or parasympathetic divisions of the peripheral autonomic system?

DIABETES INSIPIDUS

Because posterior pituitary extracts in many cases very effectively control the polydipsia and polyuria of diabetes insipidus it has become widely believed that in some way the posterior lobe controls water metabolism in the body. Most convincing are the experiments of Verney (49). This worker arranged a preparation in which the circulation of the head of a dog could be switched in and out of a heart-lung-kidney circulation, and this could be done before and after removal of the hypophysis from the head. With the hypophysis present, switching the head into the circulation reduced the urine flow; with the hypophysis removed the same procedure had no effect on urine flow. Therefore it was concluded that the hypophysis was liberating an anti-diuretic substance.

However, it has been found that complete hypophysectomy, if performed with certain precautions, is not often followed by permanent polyuria.

Then came the well-known experiments of Camus and Roussy (16), of Bailey and Bremer (11), Houssay and Hug (30), Richter (40), and others, who showed that diabetes insipidus may be produced by experimental injuries to the hypothalamus which do not involve the hypophysis. Most of these workers failed to recognize the fact that the pars tuberalis in many animals spreads out under the brain from the optic chiasm to the mammillary bodies, that it is impossible to remove this lobe without injury to the brain, and that it is *not* removed in careful operations for the so-called "complete" hypophysectomy, such as the one devised by P. E. Smith (43) for the rat.

A critical examination of the figures of Bailey and Bremer (11) shows that in most cases their incisions to injure the hypothalamus passed

through the pars tuberalis. This possibility was recognized by Curtis (19), who pictures an injury which produced a prolonged diabetes insipidus in one of his dogs. The injury had caused a defect in the floor of the third ventricle, which was closed by the pars tuberalis.

Of considerable interest in this connection are comparisons made by the writer (8) on the antidiuretic effects of pars tuberalis and pars intermedia extracts in the intact rabbit. Extracts of the posterior pituitary, or of the pars intermedia alone, commonly produced first a cessation of urine flow followed some time later by a moderate diuresis. A rise of blood pressure usually accompanied the early stages. Extracts of the pars tuberalis, on the other hand, caused neither antidiuretic nor pressor responses but almost immediately called forth a pronounced diuresis.

Trendelenberg (48) found that after hypophysectomy extracts of the tuber cinereum contained greatly increased amounts of diuretic substances. He believed that these were produced by a compensatory overactivity of the persisting pars tuberalis.

Bourquin, in a series of papers (13, 14, 15), has shown that diuresis is produced by superficial injuries to the hypothalamus but that it is abolished by deeper destruction. She consequently concludes that diabetes insipidus is an irritative and not a deficiency phenomenon.

Diabetes insipidus has been observed a number of times following epidemic encephalitis (29, 45). Eaves and Croll (23) have studied the brains in ten cases of epidemic encephalitis and find that diabetes insipidus apparently does not occur when the pathological disturbances of the hypothalamic region are severe; it is more likely to occur when they are less severe. Thus they also are led to conclude that the condition is due to an irritative rather than a destructive lesion of the brain floor.

A recent report by Whitehead and Darley (50) describes another case of diabetes insipidus of more than average severity which evidently had its origin as a sequel to epidemic encephalitis.

FROEHLICH'S SYNDROME

Fröhlich's syndrome, or adiposity and genital underdevelopment, was formerly ascribed to insufficiency of posterior lobe secretion. Recent experiments render this view untenable. Careful removal of the posterior and anterior lobes, without disturbance above the diaphragma sellae (43, 44), does not produce adiposity; while supra-sellar injections of chromic acid produce an obesity which is sometimes very marked.

Genital infantilism, or atrophy, is produced by removal of the anterior lobe of the pituitary. The condition is alleviated in animals by the daily implantation of anterior lobe substance.

It seems necessary, therefore, to believe that the adiposity of Fröhlich's syndrome is due to suprasellar disturbances involving the hypothalamus or the pars tuberalis, or both; and that the genital infantilism is due to lack of one of the hormones of the anterior lobe.

Time does not permit us to consider temperature regulation, diabetes mellitus (of cranial origin), abnormal sleep or the numerous other conditions which have been ascribed to disturbances of the hypophysis or of the hypothalamus.

In conclusion, then, one is led to stress the need for further careful experiments on animals and for critical and discriminating study of patients in order that the function of this important and intricate region, concerning which at present so much of speculation is rife, shall come to be more clearly understood. In particular need of further investigation are the functions of the pars tuberalis of the hypophysis, and the vascular and nervous interrelations of the several parts of this region.

SUMMARY

1. Current views concerning the functional relationships of the pituitary and the brain are critically reviewed.

2. It is held that adequate proof of many of these views is lacking, and that there has been a confusion of propinquity with functional association.

3. Experiments on amphibia indicate that contact of brain and pituitary fundament is necessary for the early development and differentiation of the pars intermedia, but not for the later functioning of this lobe.

4. The adiposity of Fröhlich's syndrome is probably due to suprasellar disturbances involving the hypothalamus or the pars tuberalis, or both; genital infantilism is apparently due to lack of one of the hormones of the anterior lobe.

5. Evidence indicating the possible participation of the pars tuberalis in the production of diabetes insipidus is considered.

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RENAL FUNCTION IN EXOPHTHALMIC GOITER AND MYXOEDEMA

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The morbid physiology of thyrotoxicosis and myxoedema has been extensively studied, particularly those aspects of it which deal with the cardiovascular system, the blood, and inorganic salt and general metabolism. Very little attention has been paid to the functional activity of the kidneys in these two conditions in spite of the fact that Fenwick (1), who shared with Murray the introduction of thyroid administration in myxoedema, was more impressed with the diuretic than with any other action of the gland substance.

On theoretical grounds one would expect a difference in the renal activity of exophthalmic goiter and myxoedema because of a number of circulatory antitheses, namely, the volume flow of blood (2), the circulation rate (3), the pulse rate, the pulse pressure, and the plasma volume (4). All these factors should tend to increase the renal function in exophthalmic goiter and to decrease it in myxoedema. The only data on this subject that we have found in the literature are some average figures by Lawrence and Rowe (5), who found that in a group of patients with thyroid hyperfunction the average phthalein excretion was 59 per cent and in a group with hypofunction the average was 53 per cent.

The present investigation was undertaken mainly because of the studies of Aub and his co-workers (6), on calcium-phosphorus metabolism. These investigators noted that urinary and fecal calcium excretions are very high in exophthalmic goiter and low in myxoedema. In recent experiments (7), Aub showed that the excess of calcium excretion is not affected by intake of large doses of vitamin D. The differences, however, could be explained on assuming differences in permeability. Loeb (8) mentions experiments by Embden and by Asher to indicate that thyroid alters the permeability of membranes.

The suggestion was made by Dr. J. C. Aub that some knowledge of cell permeability might be obtained from a study of the phenolsulphonephthalein elimination in a series of patients with exophthalmic goiter and in a series with myxoeodema on the basis that differences in permeability will affect the amount of dye eliminated. This has been done and the results form the subject of this report.

Method: The phenolsulphonephthalein test of renal function as described by Rowntree and Geraghty (9) was used. With few exceptions the dye was injected intramuscularly. The determination of the output

was made on the urine specimen collected two hours and ten minutes after the injection. The results of the tests were correlated with various factors, such as age, basal metabolic rate, red blood cell count, hemoglobin content and pulse pressure.

Material: A total of 75 patients with exophthalmic goiter and 22 patients with myxoedema were tested by the method described. The male patients numbered 25 with exophthalmic goiter and one with myxoedema. Sex was not a factor in determining the level of renal function. The results for the phthalein excretion according to age are recorded in Table 1 for exophthalmic goiter, and in Table 2 for myxoedema.

TABLE I

THE PHTHALEIN EXCRETION ACCORDING TO AGE OF 75 PATIENTS WITH EXOPHTHALMIC GOITER

Renal Function Per Cent	Age (Years)						
	10–19	20–29	30–39	40–49	50–59	60–69	Total
–30	..	..	..	1	1	1	3
30–39	..	..	..	1	1	..	2
40–49	..	4	3*	1	2	3*	13
50–59	2	6	7*	2	2	..	19
60–69	2	9	9	5	3	..	28
70–79	..	3*	2	1	..	..	6
80+	..	..	2	1	1	..	4
Total	4	22	23	12	10	4	75
Average	56.3	57.0	57.8	55.0	50.7	37.5	55.0

Standard Deviation of Renal Function = 13.0
Standard Deviation of Age ..... = 12.9

*Intravenous method of administration in one case.

TABLE II

THE PHTHALEIN EXCRETION ACCORDING TO AGE OF 22 PATIENTS WITH MYXOEDEMA

Renal Function Per Cent	Age (Years)					
	–30	30–39	40–49	50–59	60+	Total
–40	..	1	..	1	1	3
40–49	1	1	2	1	2	7
50–59	..	1	7	2	..	10
60–69	..	..	..	..	..	..
70+	..	..	1	..	1	2
Total	1	3	10	4	4	22
Average	40.0	45.0	51.3	43.8	46.3	47.6

Standard Deviation of Renal Function = 10.0
Standard Deviation of Age ..... = 12.3

Because of lack of comparable data for normal people, it is impossible to say how much the results obtained are above or below normal. It is clear, on comparing the average elimination of each age group, that patients with exophthalmic goiter have a higher renal function than those with myxoedema. The age group of 60 and over is an exception. Although the difference for each age group is small and not significant by itself, the

fact that there is a consistent difference in the same direction for most of the age groups, is of importance. It is difficult to explain the result for the exceptional group.

Another significant finding in exophthalmic goiter, as seen in Table 1, is the diminution in phthalein excretion with age. Actually the results show a more or less constant elimination during the ages 10 to 39, a slight decrease in the age group 40 to 49, and a more rapid falling off after 50. For example, in the age groups under 40, none of the patients excreted less than 40 per cent of the dye, and seven, or 14.3 per cent excreted 70 per cent or more of the dye, whereas, in the groups of 50 and over, three, or 21.4 per cent, excreted less than 40 per cent of the dye and one, or 7.1 per cent, excreted 70 per cent or more. Mathematically, this relationship may be expressed by the coefficient of correlation,* which is -0.29 ± 0.072—a significant correlation. The cases of myxoedema do not show this correlation, but that may be because of the fact that it is difficult to establish an association in such a small number of cases.

The importance of the relationship between age and phthalein excretion in exophthalmic goiter is that in making the comparison with myxoedema, the age distribution of the patients must be taken into account. In Table 3, the incidence of the various degrees of phthalein excretion in

TABLE III

THE INCIDENCE OF THE VARIOUS DEGREES OF PHTHALEIN EXCRETION IN EXOPHTHALMIC GOITER AND MYXOEDEMA

	Exophthalmic Goiter Per Cent	Myxoedema Per Cent	Exophthalmic Goiter (Corrected)* Per Cent	Myxoedema (Corrected)* Per Cent
Low	6.7	13.6	8.1	8.8
Low Normal	17.3	31.8	18.5	27.1
Normal	62.7	45.5	59.9	54.5
High	13.3	9.1	13.4	9.4

*Corrected for the age distribution of the combined groups as standard.

exophthalmic goiter and myxoedema is compared. The normal excretion is arbitrarily assumed to be 50 to 69 per cent and the low normal as 40 to 49 per cent. In addition, the results for each disease are corrected for the age distribution of the combined material as standard, on the assumption that age and renal function bear the same relationship in both conditions. The uncorrected results show a greater elimination of phthalein in exophthalmic goiter than in myxoedema, confirming the impression obtained above from analysis of the average phthalein excretion. They must be interpreted with caution because they are subject to large errors of sampling. The differences, though still present, are greatly reduced when the correction for age is made.

It may be argued that the kidneys excrete phthalein much faster in exophthalmic goiter than in myxoedema, although over a period of two

*Since the relationship is probably curvilinear, the correlation ratio would define it more accurately and would be greater than the coefficient of correlation. However, since the latter is significant, it serves our purpose.

hours the total excretion may amount to the same. To settle this point, one must obtain data of the renal function over consecutive short periods of time, as advocated by Shaw (10). In the four cases of exophthalmic goiter and the three of myxoedema that we have done this, the differences were slight.

In addition to age, such factors as basal metabolic rate, red blood cell count, hemoglobin content and pulse pressure in relation to renal function were studied. The results are listed in Tables 4, 5, 6, 7 and 8. With one

TABLE IV

THE PHTHALEIN EXCRETION ACCORDING TO BASAL METABOLIC RATE OF 75 PATIENTS WITH EXOPHTHALMIC GOITER

Renal Function Per Cent	Basal Metabolic Rate (Per Cent Above Normal)								
	-20	20-29	30-39	40-49	50-59	60-69	70-79	80+	Total
-30	..	..	1	..	1	..	1	..	3
30-39	..	..	..	1	1	..	..	..	2
40-49	..	..	2	4	2	3	2	..	13
50-59	1	1	6	5	3	2	..	1	19
60-69	1	5	7	7	3	3	..	2	28
70-79	..	1	..	3	1	1	..	..	6
80+	..	..	..	2	1	..	..	1	4
Total	2	7	16	22	12	9	3	4	75
Average	55.0	60.7	53.0	57.5	51.7	55.0	36.7	63.8	..

Standard Deviation of Basal Metabolic Rate* = 14.3

*In this and in subsequent tables for exaphthalmic goiter, the standard deviation of renal function is the same as in Table I.

TABLE V

THE PHTHALEIN EXCRETION ACCORDING TO RED BLOOD CELL COUNTS OF 75 PATIENTS WITH EXOPHTHALMIC GOITER

Renal Function Per Cent	Red Blood Cells (Millions)							
	4.00-4.24	4.25-4.49	4.50-4.74	4.75-4.99	5.00-5.24	5.25-5.49	5.50+	Total
-30	1	..	1	..	1	..	..	3
30-39	1	..	..	..	1	..	..	2
40-49	1	..	4	6	..	2	..	13
50-59	1	1	6	3	5	2	1	19
60-69	2	2	2	5	11	3	3	28
70-79	2	..	1	2	1	..	..	6
80+	1	..	1	..	2	..	..	4
Total	9	3	15	16	21	7	4	75
Average	53.9	60.0	51.7	53.8	58.0	54.3	57.5	..

Standard Deviation of Red Blood Cells = 0.40

or two exceptions, no definite relationship between renal function and these factors was found in either condition. In exophthalmic goiter, the incidence of low renal function tends to vary directly with the metabolic rate. For example, only 12 per cent of the patients with metabolic rates less than plus 40 had renal functions below normal (under 50), whereas 37.5 per cent of the patients with metabolic rates of plus 60 and over had the

TABLE VI

The Phthalein Excretion According to Hemoglobin Content of 75 Patients with Exophthalmic Goiter

Renal Function Per Cent	Hemoglobin (Per Cent)					
	50–59	60–69	70–79	80–89	90+	Total
–30	..	..	1	2	..	3
30–39	..	1	1	..	..	2
40–49	1	..	6	4	2	13
50–59	..	2	5	11	1	19
60–69	1	3	12	11	1	28
70–79	..	..	2	3	1	6
80+	1	..	1	2	..	4
Total	3	6	28	33	5	75
Average	61.7	51.7	54.3	55.4	57.0	..

Standard Deviation of Hemoglobin = 8.8

TABLE VII

The Phthalein Excretion According to Pulse Pressure of 74 Patients with Exophthalmic Goiter

Renal Function Per Cent	Pulse Pressure (mm. Hg.)								
	–50	50–59	60–69	70–79	80–89	90–99	100–109	110+	Total
–30	..	1	1	..	..	..	..	1	3
30–39	..	..	..	..	2	..	..	..	2
40–49	..	1	1	5	5	1	..	..	13
50–59	..	5	6	1	1	2	2	1	18
60–69	1	5	8	4	2	4	3	1	28
70–79	1	..	3	2	..	..	..	..	6
80+	..	..	..	1	3	..	..	..	4
Total	2	12	19	13	13	7	5	3	74
Average	67.5	51.7	56.9	56.9	53.1	56.4	57.0	43.3	..

Standard Deviation of Pulse Pressure = 16.6

TABLE VIII

Data on 22 Patients with Myxedema

Number	Age	Renal Function	B. M. R. Level	R. B. C. (Millions)	Per Cent Hemoglobin	Pulse Pressure
1	43	50	—34.6	4.0	70	25
2	50	40	—34.0	3.2	55	42
3	32	35	—44.7	4.2	65	25
4	24	40	—20.0	3.0	50	52
5	33	45	—30.0	3.8	60	45
6	49	50	—20.0	4.5	80	65
7	45	70*	—37.0	2.7	55	60
8	43	40*	—28.0	3.3	65	50
9	47	55	—17.1	4.3	60	65
10	73	30	—23.0	1.5	35	45
11	46	58*	—27.8	3.8	70	50
12	42	50	—19.3	4.5	75	40
13	63	70	—19.4	2.7	60	55
14	49	50	—30.8	3.6	80	66
15	49	50	—21.0	4.9	70	60
16	70	45	—28.5	4.0	60	80
17	45	40	—42.9	3.5	65	45
18	59	50	—37.5	2.7	60	35
19	36	55	—31.0	4.5	65	50
20	56	35	—34.0	4.5	70	40
21	56	50	—33.8	4.5	90	60
22	70	40	—20.3	4.8	90	60

*Intravenous.

same degree of renal function. The other degrees of renal function fail to show this relationship. In myxoedema there is a probable correlation between renal function and pulse pressure, the coefficient of correlation being $+0.41 \pm 0.125$ or 3.3 times its probable error.

SUMMARY

In a study of the phenolsulphonephthalein excretion of 75 patients with exophthalmic goiter and 22 patients with myxoedema, it was found that renal function in the former varies with age, i.e., up to the age of 50 the function is more or less constant, but after 50 it diminishes rapidly.

The renal function of myxoedema patients is slightly but consistently lower than that of exophthalmic goiter patients in all age groups except in the group 60 years and over. The function in both diseases is probably within normal limits. The slight differences are adequately accounted for by the antithetical circulatory conditions.

There is no relationship between the degree of phthalein excretion in exophthalmic goiter and myxoedema and the basal metabolic rate or the degree of anemia. There is a slight relationship between phthalein excretion and pulse pressure in myxoedema only.

The data presented offer no support to the concept that permeability of renal tissue is significantly altered in hyperthyroidism or myxoedema.

We are indebted to Dr. James H. Means for supervision of this work and to Dr. Carl F. Doering, of the Department of Vital Statistics, School of Public Health, Harvard University, for guidance in the statistical treatment of the data.

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A TECHNIQUE FOR HYPOPHYSECTOMY OF THE RAT

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The hypophysectomized rat has become of great value as a test animal in studies of the pituitary gland and its relations to the other organs of internal secretion. To be of greatest usefulness, a large number of these animals is desirable. However, in our attempts to product a colony of hypophysectomized animals the available descriptions proved inadequate, and it was found necessary to modify the various techniques in order to develop an operation which was simple and rapid, and yet which totally removed the gland. The need for large numbers of these test animals seems to justify the following detailed account of the procedure, which aims to remove the anterior and posterior lobes of the hypophysis, leaving the pars tuberalis, the pituitary stalk, and the diaphragma sellae intact.

Phillip E. Smith (4), in 1930, described a parapharyngeal approach for hypophysectomy of the rat, and in the same year Richter and Wislocki (3) suggested improvements in the method.

Recently Koyama (2) has published an ingenious method for aspiration of the hypophysis by a needle inserted through the auditory canal. However, when one recalls how difficult it is at times to secure complete ablation under direct observation, one suspects that such blind aspiration may frequently leave a pituitary residue, which will lead to inconstant experimental results. The present method provides a simplified operative approach for aspiration of the gland under direct observation.

ANIMALS

The animals of choice are healthy, rapidly growing young rats, 40-60 days old, and weighing from 80-120 grams. Their diet should receive special attention, because we have found in the course of other experiments to be reported later, that when given an "adequate" stock diet 64 per cent of a group died of various causes, whereas when given a diet rich in vitamins and growth-promoting substances, only 35 per cent of a similiar group succumbed.

ANESTHESIA

Intraperitoneal "Dial" (1)*, in dosage of 0.05 cc. per 100 grams of is advisable to assay the dosage against several different age groups in rat, is used for anesthesia. The preparation is exceedingly potent, and it order to ascertain the actual amount of the drug required to produce the

*The liquid preparation of "Dial," or "Dial-Ciba," contains diallyl barbituric acid dissolved in a small amount of mono-ethyl urea and urethane.

desired effect. The degree of anesthesia most satisfactory is that which preserves an active pharyngeal reflex. Adequate operative relaxation is induced in 15-20 minutes, and it lasts about two hours, after which time the animal begins to move about, recovering in about eight hours.

APPARATUS

A binocular telescopic magnifier (X 3), attached to a large magnifier stand with a fine focussing mechanism, is used for the dissections, and illumination is secured by a long magnifier lamp attached to the binocular. The instruments are scalpel, curved and straight forceps, small straight scissors, number six and number ten dental burrs, and four selected dental tools (Fig. 1). Suction is delivered through a glass tube which has been

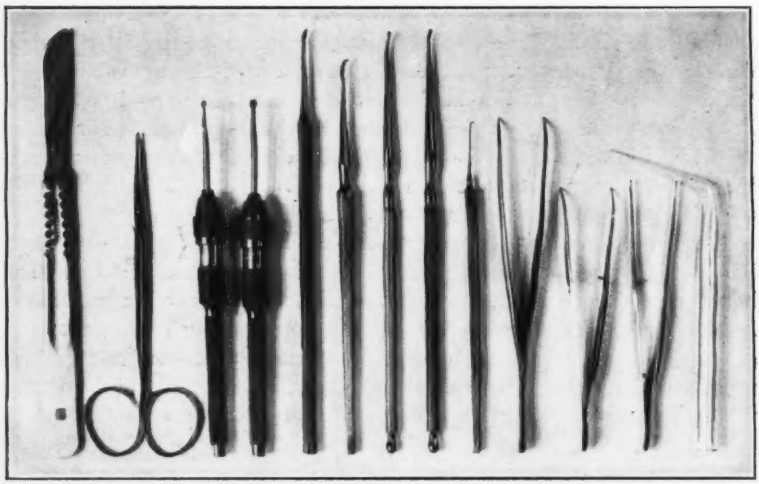

Figure 1. Instruments used in experimental hypophysectomy.

curved and drawn out to convenient size. Cotton dental pellets are used for sponging. Retractors for the subcutaneous tissues are made of copper wire, adjusted on rubber bands attached to the edge of the rat board.

General cleanliness may be substituted for surgical asepsis, because the rat is quite resistant to the common wound infections.

OPERATIVE PROCEDURE

The rat is immobilized on his back on a simple rat board, and the head and neck are kept well extended by means of a tight rubber band looped over the upper incisors. The neck is shaved and cleansed with alcohol. An incision 2.5 cm. in length is made in the midline of the neck extending caudally from the mandibular papilla. Subcutaneous tissues and salivary glands are separated in the midline by blunt dissection, and the pretracheal and digastric muscles are cleared of their thin arcolar

tissue coverings. Retractors are then placed laterally so as to expose the entire field (Fig. 2). The anterior belly of the right digastric muscle is defined and divided 1 cm. from its central tendon, and the portion attached to the central tendon is then dissected free, removed at the central tendon, and saved for use in event of later hemorrhage. The small nutrient artery of the muscle occasionally bleeds, but this may be quickly controlled by the fragment of muscle applied with gentle pressure to the bleeding point.

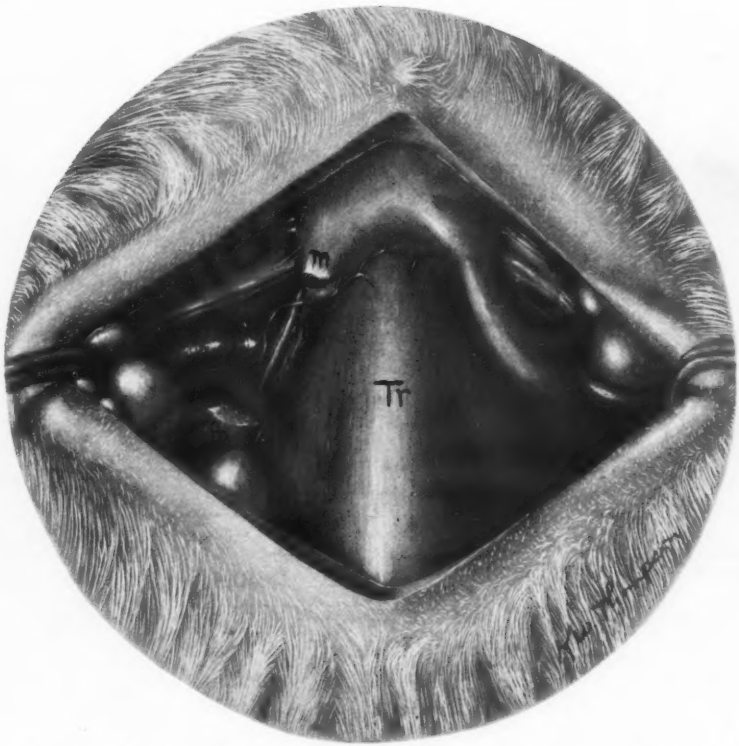

Figure 2. View of operative field. (X 3.) M. m. Venter ant. m. digastricus dextra, partially excised. N. Glossopharyngeus. Tr. Trachea. The dotted line indicates where to start the line of cleavage for view of base.

When the field is completely dry one sees the right glossopharyngeal nerve as a prominent, white, thread-like structure (Fig. 2). The nerve is gently freed from its sheath, and is pulled laterally, while a pair of smooth, curved forceps in the left hand seeks the plane of cleavage between the right borders of the hyoglossus and middle constrictor muscles and the median border of the lateral cervical muscles. This plane of cleavage may be developed to reach the midline of the base of the skull at the occipitosphenoid crest, in between the two large ethmoid bullae, and it terminates

anteriorly at the occipito-sphenoid synchondrosis, where the parapharyngeal fascia is quite adherent. Exposure is now secured by gentle traction on the trachea with a pair of curved forceps held in the right hand, and on the lateral muscles with the suction tube held in the left hand (Fig. 3). Since complete retraction closes the airway, only short interrupted glimpses may be obtained. Preparation for the burr hole is made by clearing the muscle and fascial attachments from the anterior portion of the midline

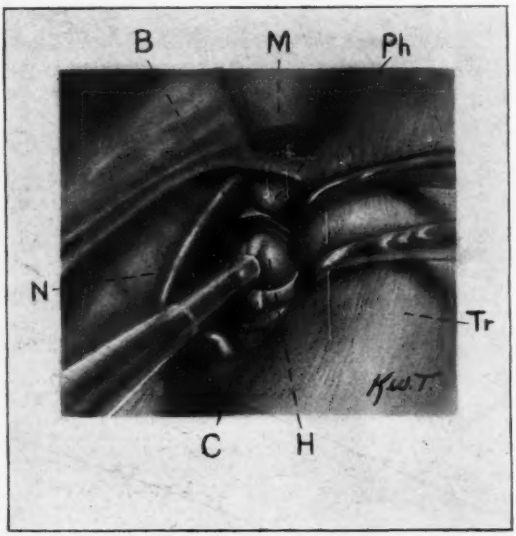

Figure 3. Exposure of the Hypophysis. (X 7.) B. Burr hole, anterior margin. C. Crista occipitalis. H. Hypophysis. M. Venter ant. m. digastricus dext. N. Glossopharyngeus. Ph. Pharynx. Tr. Trachea.

ridge with a flat-tipped dental probe, thus mobilizing the trachea and esophagus to some extent, and allowing the pharynx to be pushed anteriorly.

The burr hole is made in the midline at the anterior portion of the ridge, just posterior to the occipito-sphenoid synchondrosis (Fig. 4). Variation due to age must be allowed for, since the ridge extends farther forward in older rats. The tendency in these older animals is to place the burr hole too far forward, with the danger of entering the pharynx, and of encountering serious bleeding from the sinuses of the bone. Drilling is centered and started with a number six dental burr, and is completed with a number 10 burr, being carried almost but not completely through the bone. Ordinarily there is little bleeding, as the bone debris plugs the sinuses, but if bleeding does occur it may be quickly stopped by the use of muscle.

When the field is dry the remaining film of bone is lifted away with a sharp dental pick. The pituitary body will be seen as a light pink mass,

while the white tip of the medulla is sometimes seen at the posterior margin of the burr hole (Fig. 3). A small hook is used to tear the capsule, and suction quickly carries the gland away, usually in two portions. A deep, dark cavity remains with a glint of shiny membrane in the background, the surface of the diaphragma sellae. If bleeding occurs the slip of muscle may be inserted into the cavity for a moment. A small, blunt, right-angled hook is then used to probe the under surface of the burr hole, to make sure that no bony spicules have been pushed inward, carrying fragments of the gland out of view.

When complete removal has been assured by inspection and by exploration, a small portion of the muscle is placed in the pituitary fossa to prevent recurrence of hemorrhage after closure. The tissues are allowed to fall back, and all blood clot is washed out with wet saline pellets. The

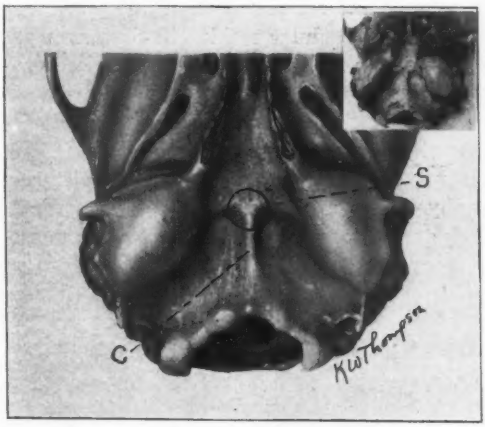

Figure 4. View of the base of the rat's skull, the circle indicating the site for the burr hole. (X 5.) The insert is a natural size photograph. C. Crista occipitalis. S. Synchondrosis sphenooccipitalis.

skin incision is closed with interrupted number A silk sutures passed on straight milliner's needles. Mucus which has accumulated in the mouth and pharynx should be removed by suction, before the rat is placed in his cage. Recovery of old, pregnant, or unfavorable animals is often aided by giving a subcutaneous injection of 10-15 cc. of Ringer's solution.

POSTOPERATIVE CARE

These animals now require great care, presumably because of their pituitary deficiency. They should be placed in open cages in a warm room, with small jars of food and water easily available. Mucus accumulating in the air passages should be removed by suction. This accumulation of mucus is much more likely to be serious with older or pregnant rats, or with those who have had much damage to pharynx or trachea. Younger animals recover from the operation in a short time, being quite active in

24 hours, but older rats recover more slowly, and never become very active. The skin incision will heal within a week or so, and the silk stitches need not be removed, unless the rat is segregated, because the other rats will perform this operation.

EVIDENCE OF COMPLETE REMOVAL

Serial section of the pituitary fossa after autopsy is the only absolute evidence of complete removal of the gland. However, the changes which take place in the animal surviving hypophysectomy are now well established, and the typical dwarfism, diminished heat production, the soft, fluffy fur, atrophy of the testes in the male, and persisting dioestrous vaginal smear in the female, all give strong evidence of complete removal. Continuous records of these factors will indicate the success of the operation in individual cases. This plan has been carried out with all our rats, and subsequent autopsy and serial section of the pituitary fossa has confirmed the presence of a glandular residue in those animals that have not had the typical course. A small spicule of bone projecting inward, usually on the right, protecting a portion of the gland from the suction, seems to be the principal cause of these incomplete hypophysectomies. When this observation was made the manoeuvre for probing the under surface of the burr hole margin was initiated, and since that time there have been fewer incomplete hypophysectomies. Among the first hundred there were eight rats whose record and autopsy showed incomplete removal, while in the second hundred there were only three.

DISCUSSION

The principal advantage of this technique lies in the operative approach, which allows a good view of the hypophysis, and yet avoids an opening into the pharynx, with the complications of bleeding into the air passages. The very small tunnel for the view of the base of the skull, with the possibility of accurate localization of the site for the burr hole, diminishes the risk of the procedure. Emphasis of the importance of only short glimpses, avoiding prolonged closure of the airway, prevents fatalities from asphyxia as well as damage to the trachea and resultant postoperative production of mucus. Round burrs of two sizes permit drilling accurately in the midline, and their debris effectively plugs the blood sinuses of the bone, so that hemorrhage seldom occurs at this stage unless it is accidentally provoked by too generous use of the suction. The small slip of muscle removed early in the operation, if advantageously used, controls nearly all hemorrhage. "Dial" is more convenient than ether as anesthetic, when an assistant is not available.

The disadvantage of the operation lies in the danger of injury to the medulla, which actually seldom occurs if the burr hole is properly placed. Occasionally the meninges over the medulla are opened, and cerebro-spinal fluid escapes. This does not seem to cause any alteration in the subsequent course of our rats, for they appear the same as those described by Smith

(4), in whose operation the cerebro-spinal spaces are presumably not entered.

With practice and care the operative mortality should be low. We have not kept an accurate record of mortality, except for the last fifty rats, in which it was ten per cent. The hypophysectomized rats are exceedingly delicate, and usually about 35 per cent of the animals die within a few weeks because of acute respiratory infections, diarrhoea, or otitis media with labyrinthitis. Older individuals occasionally die during the first few days from what is probably cachexia. Under ideal conditions of heat regulation, isolation, and diet, the postoperative mortality can be materially lowered.

SUMMARY

A technique for hypophysectomy of the rat has been described. The principal advantages of the method are:

1. Accurate localization of the site for the burr hole is possible.
2. The pharynx is not opened during the operation.
3. The operative defect is small, minimizing trauma to the tissues.
4. Danger of hemorrhage is less, due to the use of muscle and due to the plugging of sinuses with the debris produced by round burrs.
5. The intraperitoneal anesthesia used is somewhat more convenient than ether.
6. The time consumed in the operation is short, averaging from 10-15 minutes.

NOTE:—I wish to thank Dr. Harvey Cushing for the opportunity of doing this work, and Dr. Richard Meagher, Resident Surgeon of the Peter Bent Brigham Hospital, for his suggestions which accelerated early progress.

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A THYROID HORMONE IN THE BLOOD AND URINE IN GRAVES' DISEASE

(PRELIMINARY PAPER)

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In a previous communication (1) we offered evidence in support of the diagnostic significance of lymphoid tissue in exophthalmic goiter. We felt at that time, and so stated that experimental methods must be invoked before more light could be thrown upon the subject. Weller (2) in 1930 called attention to liver damage seen in cases of exophthalmic goiter coming to necropsy. He reported control studies on 44 cases of Graves' disease and was able to show a high incidence of chronic parenchymatous hepatitis in this disease. Weller's observations suggested a possible basis for experimental methods in the study of thyroid disease. Added stimulus for the hope of an experimental procedure was furnished by the work of Dresel (3, 4) and his associates, who in 1929 described a method for detecting thyroid substance in the blood. By injecting mice with blood serum from patients suffering from Basedow's (Graves') disease they were able to demonstrate a disturbance of liver function, perhaps the first stage of the liver disorder described by Weller and others.

Dresel injects mice with serum from the patient and forty-eight hours later after a fast period the mice are killed and the liver tested for the presence of glycogen. This is done by grinding the liver tissue in a mortar with sand, precipitating out the proteins with trichloracetic acid and testing the filtrate for glycogen with Lugol's solution. Assuming that the disturbance in glycogen function is a constant feature of true Graves' disease, we felt that the phenomenon could possibly serve as a means of further studying the significance of lymphoid tissue and adenomatous structures in the thyroid gland. Using this method and modifications, details of which will be given in a subsequent publication, we have tested the blood and studied histologically 24 surgical cases diagnosed clinically as exophthalmic goiter with results shown in Table 1.

TABLE 1

Lymphatic tissue present histologically Hormone test positive	13
Lymphatic tissue absent histologically Hormone test negative	7
Lymphatic tissue present histologically Hormone test indefinite	2
Lymphatic tissue present histologically Hormone test negative	2
	24

Of the seven thyroids showing no lymphatic tissue with a negative hormone test, five showed degenerating adenoma with nodular goiter, while two showed no definite disorder. The two glands showing lymphoid tissue to be present, but giving an indefinite hormone test were markedly iodized. We have no explanation at this time, for the discrepancy represented by the two cases showing negative hormone tests in the presence of undoubted Graves' disease.

During the progress of this work an article by Willis and Mora (5) appeared in which they report the use of Dresel's method as a diagnostic test. They call attention to the possible influence of iodine therapy on the reaction and this may possibly explain some of the indefinite and untoward results.

Inasmuch as most foreign substances in the body are excreted through the kidneys, we considered the possibility of demonstrating the thyroid hormone in the urine. Accordingly, urine specimens were obtained from the last 17 subjects and tested on mice. The results are given in Table 2, and demonstrate beyond a doubt the presence in the urine of this substance which, when injected into mice, deprives the liver of its glycogen.

TABLE 2

No. of Expt.	*Lymphatic tissue (Graves' disease)*	*Hormone test on serum*	*Hormone Test on urine*
8	Not present	Negative	Negative
9	Present	Positive	Positive
10	Present	Positive	Indefinite
11	Present	Positive	Positive
14	Present	Positive	Positive
15	Not present	Negative	Negative
17	Present	Indefinite	Positive
18	Present	Positive	Positive
19	Present	Positive	Positive
20	Present	Positive	Positive
22	Present	Positive	Positive
23	Present	Negative	Positive
24	Present	Positive	Positive

Four mice died before the completion of their experiments. The cause of death in these cases is not known. In one case a non-catheterized specimen of urine was used which may have been responsible for infection. There is also the question of extreme toxicity of the specimen, due to the Graves' disease hormone, to be considered since all experiments in which the mice died were from subjects of undoubted Graves' disease.

Forty specimens of normal blood serum were used in experiments on mice and in no case was the glycogenic function of the liver in the injected animal disturbed. On the other hand, in experiments with thirty supposedly normal urine specimens two gave results similar to those obtained in cases of Graves' disease. One case of carcinoma of the cervix gave a positive result in the urine but the blood was normal. In eight other cases of malignant neoplasm both blood and urine were normal.

The nature of the substance is being studied, as is also its permanency in the blood and urine after thyroid resection. The procedure is now being used in connection with animal experiments on thyroid disease.

SUMMARY

When the blood serum or urine from patients with Graves' disease is injected into mice a substance capable of disturbing liver function can be demonstrated. In the limited number of cases studied, the presence of the hormone parallels the presence of lymphoid tissue in the resected thyroid glands, thus lending further support to the view that lymphoid areas are an essential part of the pathological picture in Graves' disease. It is suggested that the demonstration of this hormone in urine or blood serum might be useful as an aid in differential diagnosis and also prove to be of value in the experimental study of Graves' disease.

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STUDIES ON THE EXTRACTION OF THE TESTICULAR HORMONE FROM TISSUES AND ON ITS QUANTITATIVE DISTRIBUTION THEREIN*

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In this paper we are presenting the results from studies on the following aspects of the testicular hormone problem:

A. Attempts to improve the yield of the comb growth stimulating hormone from testis tissue.

B. The significance of the irregular yield of the hormone from ram testicles.

C. The relation of the age of the animal to the concentration of the hormone in bulls' testes.

D. The examination of blood and plant tissues for this testicular hormone activity.

A. ATTEMPTS TO IMPROVE THE YIELD OF THE COMB GROWTH STIMULATING HORMONE FROM TESTIS TISSUE

One of the most striking facts in this field of endocrinology is the extremely small yield of hormone obtained by our present methods of extraction of testis tissue. Not only is the weight of the final active material very low but, physiologically speaking, the amount of activity also appears ridiculously low per unit weight of material. In the earlier studies by McGee (1, 2) in this laboratory, it was found necessary to use for the daily injection per capon, the equivalent of 150 to 250 grams of the fresh bull testicle tissue, but as a result of refinements in the comb growth assay method and in purification the average minimum now necessary per day to produce an appreciable growth in five days is 25 to 50 grams of fresh bull testicle tissue. The minimum amount of testis tissue necessary per daily injection still appears high for an endocrine organ. We have no reason to suspect that the relatively low yield of potency is due to loss or destruction of the hormone in the process of extraction so that we are confronted with either a tissue which contains an extremely small amount of the hormone or with a situation in which the material as we extract it may be considered to be in part in the "free form" in equilibrium with a "conjugated form" and that the latter may have other solubilities or be inactive or both. On the other hand the fact that the testicular hormone is

*These investigations were made possible in part through a grant from the Committee for Research in Problems of Sex, National Research Council.

rapidly excreted in the urine suggests that the testis must be producing the substance at a rapid rate and that it may therefore not store an appreciable amount thereof.

In attempting to increase the yield, we first took some of the tissue residue left after the usual procedure and re-extracted the same in three different ways. The results clearly show that thorough re-extraction with ether or 70 per cent alcohol yields so very little additional activity per weight of original tissue that it is not worth the extra effort.

We next carried out incubation of the fresh bull testis tissue with and without pancreatic lipase. The fresh tissue was delivered to the laboratory in the frozen condition, next it was freed from tunics, hashed and refrozen in liquid air. In this frozen condition it was ground under liquid air in a mortar. Portions of this prepared tissue were next digested at 40° C. for three days with and without pancreatic lipase in a 0.2 per cent sodium carbonate solution. Following this the routine extraction with alcohol was carried out as usual. The results simply suggest a slightly better yield after incubation with pancreatic lipase. However, before making such a claim very careful quantitative studies with many birds would need to be made. At any rate, the individual variations in the reactions of the birds to one and the same dose are of the order here observed. Unfortunately, we did not have enough birds to make this study more quantitative.

Attempts to increase the yield materially by acid hydrolysis of testis tissue likewise led to no better results. In fact, the material from the acid hydrolysis was found inactive, but very toxic, judging from the local reaction. Whether the hormone was destroyed or lost otherwise we do not know.

Our results then seem to support the view that by our routine procedure we are extracting fairly completely the available hormone found in testicular tissue and that neither enzyme nor acid hydrolysis liberates more of it.

B. THE SIGNIFICANCE OF THE IRREGULAR YIELD OF THE HORMONE FROM RAM TESTICLES

In the earlier distribution studies by Gallagher (3) in this laboratory, he repeatedly obtained negative results in attempting to extract the comb growth stimulating hormone from rams' testicles. However, in continuing these studies, we finally obtained some activity in the autumn of 1929. These irregular results, as well as the mating habits of sheep, suggested a possible seasonal variation in the concentration of the hormone in ram testis tissue. To throw light on this question we attempted to carry out quantitative studies on monthly collections of ram testicles. Unfortunately, the number of rams slaughtered in Chicago is so irregular and limited that we have not been able to carry this study through as completely and thoroughly as we had desired. The routine procedure was that of Gallagher and Koch (4), the stage of purification in this study being that of the cold acetone-soluble fraction. The results again show the low and irregular

yield of hormone and suggest a possible seasonal variation. The limited number of observations shows that the August, October, November, and March collections gave better yields than the January, February, and April collections. We realize that the results are too few to justify final conclusions and that such factors as age and breed may be involved. It is, however, true that the yield of hormone is low per unit weight of fresh tissue and that the acetone-soluble fraction containing this activity is more difficultly soluble in olive oil than the same fraction obtained from bull testicles. It is barely possible that this difficulty of solution in part explains the irregular results. Other attempted methods of extraction of the tissue, that is by acetone, ether-alcohol mixture, butyl alcohol, saponification by alcoholic sodium hydroxide, preliminary acid hydrolysis or preliminary lipase digestion, respectively, gave equally low or negative yields.

C. THE RELATION OF THE AGE OF THE ANIMAL TO THE CONCENTRATION OF THE HORMONE IN BULL TESTES

For the investigation of this question, the routine procedure of McGee (1), and Gallagher and Koch (4) was used as previously indicated. The tissues, classified as foetal, young calf (under 2 months of age), adult bull and old bull (8 to 10 years of age), were collected for us at the Wilson & Company packing plant under the supervision of Doctor Swain. We are very grateful to Doctor Swain for his aid and interest in this phase of the work. The testicles were delivered to the laboratory in the frozen condition. Before extraction, they were dissected free from tunics and epididymides with the exception of the foetal testes which were hashed without trimming.

Table I shows that the percentage yield of benzene and acetone-soluble material is higher in the foetal and young testicle tissues than in the adult and old tissues. This is true in spite of the fact that we used the untrimmed foetal testes. The very obvious preponderance of connective tissue in the old bull testes, however, would lead one to expect the observed low yield of lipin.

TABLE I

THE YIELDS OF SOLIDS EXTRACTED FROM TESTICLES OBTAINED FROM ANIMALS OF VARIOUS AGES

Preparation	Testes	Weight of Tissue in kg.	Benzene Fraction in gm.	Acetone Fraction in gm.	Per Cent Weight of Original Tissue	
					Benzene Soluble	Acetone Soluble
W24	Foetal	3.2	65.	11.5	2.03	0.36
W 4	Calf	8.0	122.0	35.62	1.52	0.44
W 9	Calf	4.5	78.0	19.62	1.73	0.43
W 1	Adult Bull	35.0	416.0	40.7	1.19	0.11
W 2	Adult Bull	18.0	220.0	24.15	1.22	0.13
W12	Adult Bull	17.0	180.0	21.3	1.06	0.12
W23	Old Bull	16.0	110.0	12.5	0.69	0.08
W33	Old Bull	6.8	48.0	7.24	0.7	0.10

Our results on the assay of the acetone-soluble material are quite irregular, to be sure, but the average values indicate a higher concentration in young and foetal testis tissue than in that of old bulls. If expressed on the basis of the minimum weight in grams of original testis tissue daily necessary to give a comb growth response in five days, the values are 15± foetal; 15 to 20 calf; 25± adult bull; and 25 to 50 old bull testis tissue. We again wish to emphasize that the quantitative relations as to activity per unit weight of original tissue are only approximately established by these observations. The presence of the comb growth stimulating principle in the foetal testis tissue is, however, definitely established. These findings are in harmony with Lillie's (5, 6) hormone theory of the freemartin in cattle and with the cytological investigations of others. Miss Chapin (7) obtained clear-cut evidence that the male sex hormone is elaborated at the time of differentiation of the gonads in foetal life, and Whitehead (8) demonstrated that in the 2.5 cm. pig embryo, the interstitial cells of the testes appear to be actively secreting and to be multiplying rapidly up to the 28 cm. length or until just before term. According to Whitehead, this activity decreases during juvenile life.

These observations on the foetal and calf testes may appear contradictory to our findings recorded in another paper that we could not find the male hormone in the urine from bull calves and from boys under ten years of age. It is, however, possible that in the pre-pubertal stage, the testes, although normal in interstitial tissue and in hormone content, may nevertheless not be secreting the hormone. In fact, the lack of typical secondary sex characters before puberty would lead one to expect little or no secretion of the male sex hormone prior thereto. If the hormone is secreted other possible explanations are that the renal threshold is higher in these young animals or that there is considerable destruction of the hormone by juvenile tissues.

D. THE EXAMINATION OF BLOOD AND PLANT TISSUES FOR THE TESTICULAR HORMONE

Blood. In 1928 Gallagher (3) demonstrated the presence of the male hormone in the testes of calves, bulls and hogs. Only one other bull tissue, the epididymis, yielded active extracts. The negative results were obtained on brain, pancreas, prostate, thyroid, suprarenal, kidney, liver, seminal vesicles and blood. In view of the established presence of this hormone in human male urine, the negative results on bulls' blood are disturbing. We have repeated the work of Gallagher, the only difference being that we carried the separation through the cold acetone-soluble stage, whereas he used the olive oil solution of the benzene soluble material.

Three gallons of fresh bull's blood were drawn into 95 per cent alcohol with continual stirring. The extraction was then carried out in the usual manner and the acetone-soluble fraction dissolved in olive oil. Two capons were injected daily with the equivalent of 150 cc. and 300 cc. of blood, respectively. On the fifth day the one on 300 cc. per day showed some

signs of comb growth, so the dose on him was increased to the equivalent of 600 cc. blood per day. On the third day following the increase in dosage, the increase in L+H of the comb was 5 mm. The other bird reacted negatively on the equivalent of 150 cc. of blood per day. The results indicate the presence of the hormone in blood but in extremely low concentration. Muto (9), to be sure, reported finding the hormone by injecting the blood taken from the spermatic vein of a mouse into a castrated mouse. He used as his test the weight of the vas deferens in the injected castrated animal as compared with the normal. This test is, however, of doubtful value so that Muto's findings should not be taken too seriously.

Plant Tissues. Five pounds of wheat, five pounds of Fleischmann's yeast and ten pounds of spinach were each extracted by our routine procedure and carried through the acetone treatment. Although large doses were injected into capons no comb growth response was obtained. The injection of an ether extract from carrots, prepared by Dr. Fred D'Amour of this department, likewise led to negative results.

Apparently the asexual parts of plants are either free from the male hormone or the concentration therein is extremely low. We have not thus far attempted to confirm the findings of Loewe and Voss (10) that the male parts of plants such as Salix caprea contain the testicular hormone while the female parts contain the female hormone. It may be recalled that a number of workers have from time to time reported finding the female sex hormone in the asexual parts of plants such as reported on here. However, in the light of our better knowledge of the individual variations of the ovariectomized rat or mouse, some of the reported positive findings should be interpreted very cautiously. More quantitative and many comparative observations must be made before we can determine the distribution of these "hormone activities" in plant tissues.

SUMMARY

1. The routine procedure of McGee, Gallagher and Koch for the extraction of the testicular hormone appears to be the most complete at present. Attempts at hydrolyzing hypothetical combinations of the hormone have not increased the yield of hormone.

2. The yield of hormone from rams' testicles was found to vary more than from bulls' testes. The limited comparative studies on monthly collections suggest a possible seasonal variation.

3. The presence of testicular hormone in foetal bulls' testes was proved. It appears to be in higher concentrations in foetal and calf testes than in adult or old bull testis tissue.

4. The concentration of the hormone in bulls' blood was found to be of the order of one-twelfth of that found in bulls' testes.

5. Attempts to obtain active extracts from wheat, yeast, spinach or carrots were unsuccessful.

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THE TESTICULAR HORMONE CONTENT OF HUMAN URINE*

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Loewe, Voss, Lange and Wähner (1) reported that by their seminal vesicle "regeneration test" on the castrated mouse, they found it necessary to use the equivalent of 3.6 liters of male urine to demonstrate the presence of the male hormone therein. Funk, Harrow and co-workers (2, 3, 4), as well as workers in this laboratory, showed that by the comb growth method testicular hormone in the urine of adult men can easily be detected by injecting the equivalent of 50 to 150 cc. of urine per capon per day. The earlier investigations (5, 6, 7, 8) in these laboratories on the extraction of the testis hormone from testis tissue naturally led us to investigate other tissues and fluids. In this paper we present some of our recent findings on human urine.

A. METHODS

We first investigated various methods for the extraction of the comb growth stimulating hormone from urine with the view of devising a comparative quantitative procedure applicable to a 24-hour sample of urine. Among the various attempts may be mentioned: (a) continuous ether extraction; (b) continuous ether extraction of the acidified urine followed by fractionation in cold acetone, resolution in ether and shaking with 10 per cent NaOH; (c) butyl alcohol extraction; (d) refluxing of urine with ether on a water bath; (e) shaking urine or concentrated urine with ether on a water bath; (f) shaking urine or concentration urine with equal volumes of benzene, ether, or chloroform; and (g) continuous extraction of acidified urine with benzene for 24 to 36 hours. The best and most consistent results have been obtained by extracting acidified urine by benzene. This method of extraction together with the treatment by 10 per cent NaOH gave the most consistent results with least toxic action on the birds.

The procedure finally adopted for these studies is the following: The urine is evaporated to one-fifth its original volume, then after adding 20 cc. of concentrated hydrochloric acid per liter of original urine, it is shaken at room temperature with an equal volume of benzene. This first benzene extract is set aside. The urine layer is then placed in a Kutscher continuous extractor and extracted for 30 to 36 hours with fresh benzene The two benzene extracts are combined and evaporated to dryness under diminished pressure, care being taken to remove the benzene as completely as possible. The residue, after dissolving in 100 cc. of ether per liter of

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original urine, is vigorously shaken with one-tenth the volume of 10 per cent NaOH. The aqueous layer is repeatedly shaken with fresh ether and the combined ether extracts evaporated under diminished pressure and taken up in the proper volume of olive oil.

For the assays we used Brown Leghorn capons which had been castrated at the age of six to eight weeks by Dr. L. V. Domm of the Whitman Laboratory of Experimental Zoology. We wish to thank Dr. Domm for this assistance. The birds were kept in large pens at the Whitman Laboratory with free access to the outdoors. The olive oil solutions of the extracts were injected subcutaneously daily for periods of five to eight days and the comb growth is recorded as the sum of the increases in length and height.

B. THE EFFECT OF AGE ON THE TESTICULAR HORMONE EXCRETION

Funk, Harrow and Lejwa (3) reported a few results which indicated that the urine from men in the prime of life contains more hormone than from old men. Our results on the hormone in testes at different ages suggested an investigation of a similar character on the relation of age to hormone excretion. We have not studied the urines of old men, but have emphasized those of children and men in the prime of life. (See Table I.)

TABLE I
ASSAYS ON MALE URINE AT DIFFERENT AGES

Fraction	Age	Source	Quantity Extracted	Daily Dosage Equivalent to Urine cc.	Bird No.	mm. Comb. Growth
62a	7 years.....	R. G.....	24 hr. S.....	72	22	0
62b	7 years.....	R. G.....	24 hr. S.....	70	987	0
69a	3 years.....	M. H.....	24 hr. S.....	75	7	0
69b	3 years.....	M. H.....	24 hr. S.....	80	11	0
K-83	4-10.....	Composite.....	6 liters.....	600	966	0
K-84a	14-20.....	High Sch.....	8 liters.....	270	20	12
K-84b	14-20.....	High Sch.....	8 liters.....	270	44	10
K-65	Adult.....	Composite.....	3400 cc.....	340	57	12
K-66	Adult.....	Composite.....	3500 cc.....	350	955	15
K-70-B1	Adult.....	Composite.....	4 liters.....	400	17	14
K-73	Adult.....	24 hr. S.....	1300 cc.....	130	57	9
K-90	Adult.....	24 hr. S.....	1000 cc.....	100	953	8
K-53	Adult.....	Composite.....	800 cc.....	80	14	6
K- 3	Adult.....	24 hr. S.....	850 cc.....	85	514	8

The extracts from individual and composite samples of urine from boys under ten years of age uniformly gave negative results. The daily injections with the individual 24-hour samples represented only 70 to 80 cc. of urine, but since the total volume of the 24-hour sample was only 500 to 600 cc., this dosage is equivalent to the injections employed of the adult urine. Furthermore, since the injection of the equivalent of 600 cc. urine daily of the composite samples gave equally negative results, these experiments seem to warrant the conclusion that the hormone concentration must be very much lower than that found in urine of men where the equivalent of 50 to 150 cc. per day is ample to give a good response in comb growth. The urines from boys 14 to 20 years of age gave values comparable to those of mature men.

The negative results from urine of boys under ten years of age may appear contradictory to our findings on the testes from foetal and two months' old calves. However, when the equivalent of 400 cc. of bull calf urine per day was injected over a period of eight days, it gave negative results. Therefore, we are inclined to think that although the immature testes contain the hormone, they are either not secreting the same or if the hormone is secreted, it must be destroyed more completely or conserved more economically as a result of a different kidney threshold than in the normal adult male. The fact that evidences of secondary sex character become evident more particularly at puberty is a physiological implication that the testes in the foetal and prepubertal stages are not secreting the hormone to the same extent as as in the adult.

C. EXTRACTION OF A COMB GROWTH STIMULATING SUBSTANCE FROM WOMEN'S URINE

Laqueur and his co-workers (9) as well as others have reported the presence of the female sex hormone in urine from normal young men. Very recently Brouha and Simonnet (10) reported that pregnancy urine up to two months' term, when injected into normal immature male rats, causes a more rapid development of the genital tract whereas in normal adult male rats it causes hypertrophy thereof. This effect they attribute to the action of the anterior pituitary hormone. As no reports have been made on female urine, we undertook to examine urine from ovariectomized, normal mature and pregnant women.

The same method of extraction as previously described was used in all of these studies. The results are given in Table II. The values obtained show that normal and pregnancy urines from adult women yield the same amount of comb growth stimulating material as urine from normal mature men. The one case of the ovariectomized woman gave two negative results, although the equivalent of 400 cc. of urine was injected. Pregnancy urine

TABLE II

ASSAYS ON FEMALE URINE EXTRACTS

Sample	Source	Bird No.	Daily Dosage Equivalent to Urine cc.	mm. Comb. Growth	Vaginal Smear Test
K-60	Ovariectomized	28	400	0	
K-62	Ovariectomized	954	400	0	
*K-63	Pregnancy	2	250	14	
K-61	Normal	995	500	18	
K-67	Normal	4	185	7	Negative
K-68	Normal	954	180	13	Negative
K-69	Normal	6	250	12	
K-71	Normal	996	220	9	Negative
K-72	Normal	46	245	11	Negative
K-74	Normal	40	98	7	
K-75	Normal	47	130	0	
K-76	Normal	45	175	5	Negative
K-77	Normal	974	245	13	
K-78	Normal	4	270	8	

*A composite sample which also gave a positive assay for female hormone according to test developed by Juhn and Gustavson.

gives an average result slightly higher than non-pregnancy urine. More studies must, however, be made before we can state this to be the general rule. The pregnancy sample here used was part of a composite sample, while the normal non-pregnancy samples were all 24-hour collections. It is worth noting that although our extract from the pregnancy sample gave the typical female feathering response as observed by Juhn and Gustavson and therefore contained female sex hormone, we nevertheless obtained almost equally good comb growth from normal female urine preparations which gave negative vaginal smear tests in the hands of Professor R. G. Gustavson and Dr. Fred E. D'Amour. In none of the other cases did we observe the female feathering after the injection of our extracts. We are inclined to interpret these comb growth reactions as due to the male hormone or to a substance possessing similar solubilities and physiological actions. That it is not the female hormone which causes this comb growth response is indicated, first by the negative vaginal smear reactions above, second by the negative comb growth response from purified theelin preparations and third, by the following personal communication from Professor R. G. Gustavson. In the course of the work reported on by Juhn, Gustavson and Faulkner (11, 12) they frequently observed comb growth as well as female feathering when the capons were injected with crude female hormone preparations from pregnancy urine while at other times the comb growth response was negative, although the female feathering response remained.

After we obtained the results here indicated, Professor Gustavson examined his protocols and found that the positive comb response was obtained only in those cases in which the purification by removal of the female sex hormone into 10 per cent NaOH was not carried out as completely as in those cases in which feather changes and positive vaginal smear tests were obtained without comb growth response. Thus, capon 29-939, which received a daily injection of 9 rat units (vaginal smear basis) per 100 grams body weight of a crude preparation from pregnancy urine from December 4 to December 19, showed an increase in comb growth of 19 mm. (L+H), while capon 29-984, with a daily injection of 400 rat units (the equivalent of 1200 cc. of pregnancy urine) of a highly purified theelin preparation, showed marked feather changes but an actual decrease in the size of the comb. We feel that the ether-10 per cent NaOH treatment, if properly carried out, actually separates from each other the female and the male hormones here under discussion. That the action is not due to anterior lobe secretion is also demonstrated by the negative comb growth response observed after two capons received daily for ten days, five times the dose of the gonad-stimulating preparations necessary to cause precocious sexual development in the immature white rat. We are indebted to Mrs. Zonja Wallen-Lawrence and Professor H. B. van Dyke of our Pharmacological Laboratory for this preparation.

We feel that our results warrant the conclusion that we have present in urine from pregnant and normal mature women, a substance very sim-

ilar to or identical with the testicular hormone, but that it is different chemically in some respects and acts differently physiologically from the female sex hormone which produces oestrus in the castrated female. The actual source and function of this hormone is at present a mystery. Although the urine from the ovariectomized woman gave negative tests, we do not regard this one case as sufficient evidence to be considered in this connection. On the other hand, Gallagher (13) in these laboratories could not find the testicular hormone in cattle ovaries, although he made three attempts.

SUMMARY

1. A method for the comparative quantitative extraction of 24-hour collections of human urine was devised.

2. No comb growth stimulating hormone was found in urine from boys under ten years of age.

3. The urine of adolescent boys yielded quantities of hormone of the same order as the urine from mature men.

4. The urine of pregnant and normal women yielded quantities of the hormone of the same order as the urine from mature men.

5. The comb growth response from pregnancy urine could not be duplicated by the action of theelin.

6. It was found that the comb growth stimulating hormone and the theelin in women's urine can be separated from each other by the ether-10 per cent NaOH treatment.

7. The quantitative aspects of the work here reported are necessarily incomplete due to the limited number of birds available and also due to the limited number of assays that can be made from a 24-hour collection of urine.

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OVARIECTOMY AND CORPUS LUTEUM EXTRACT STUDIES ON RATS AND GROUND SQUIRRELS*

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The present work on ovariectomy and the effect of the corpus luteum was begun in 1928. When Corner and Allen (1, 2, 3) reported maintenance of pregnancy in ovariectomized rabbits, our cruder method of extraction was discarded and theirs used. After the work of the junior author on rats was well under way favorable effects on the maintenance of pregnancy were reported by Harris and Pfiffner (4). For this reason the work on albino rats will be given very briefly and that of the senior author, on ground squirrels *(Citellus tridecemlineatus pallidus,* from Western Kansas), more fully.

The ovaries were removed aseptically at known intervals of time following copulation or the finding of the vaginal plug in the rats or at different sizes of the uterine enlargements in the ground squirrels which had copulated in the field before capture. Special care was taken to remove all of each ovary and if the extract appeared to aid in the maintenance of pregnancy a search was made at autopsy for any remaining ovarian tissue.

Beginning immediately after ovariectomy daily injections of 0.2, 0.3 or 0.4 cc. of the corpus luteum extract were made subcutaneously. The extract was made from sow ovaries, ground while warm and placed immediately into two or three volumes of alcohol. Corner and Allen's (1) method of extraction was followed in detail and the yields were almost the same as theirs. Two of the eight batches of extract were made with methyl instead of ethyl alcohol, as was done by Harris and Pfiffner (4), resulting in a smaller yield.§

EFFECT OF OVARIECTOMY ON PREGNANCY IN RATS

Bilateral ovariectomy performed on 11 rats from seven to eighteen days pregnant resulted in abortion in each case within 28 to 48 hours, except in one operated on at 13 days in which it took place within 60 to 72 hours. The average time was about 40 hours. Two of three animals ovariectomized at 19 days aborted in 24 to 40 hours, but one bore at full term three dead and four living young which died within 12 hours, evidently from lack of milk, as this mother was also unable to nurse young from another litter. Four rats ovariectomized at 20 days of pregnancy went to full term (22 days), each bearing some viable young (1, 3, 4, 6,

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respectively) of less weight than normal and some dead young (7, 7, 5, 3, respectively). The mammary glands were found to be functional only in one female and two of her six young were still alive after 12 hours. The young of the other ovariectomized females all died within 2 to 3 days, evidently partly because the mothers had no milk. In the two cases of removal of the ovaries at 21 days, eight living young were produced in one litter and four living and three dead in another at about the normal time, i.e., on the 22nd or 23d day. The mammary glands functioned and the young lived.

That the abortions following bilateral ovariectomy were caused by the absence of the ovarian tissue and not by any other effect of the operations was shown by the fact that unilateral operations on eight rats at 10, 11, 12, 13, 14, 19, 20 and 21 days of gestation resulted in the birth of normal viable young at full term.

EFFECT OF CORPUS LUTEUM EXTRACT WITH OVARIECTOMY ON PREGNANCY IN RATS

As no consistent difference was noted between the seven different batches of extract, including the two prepared with methyl instead of ethyl alcohol, no distinction will usually be made between them.

Of seven rats ovariectomized one to four days after copulation (before implantation) three showed some growth effect on the endometrium of the uterus with the ethyl extract and two with the methyl alcoholic extract. Two injected with the latter extract showed no effect of the extract. It cannot be certain that these had conceived since the finding of a vaginal plug is not infallible evidence of conception.

In 19 rats ovariectomized at from eight to seventeen days of pregnancy and given daily injections of the corpus luteum extract four aborted in two days after the operation, eight aborted in an average of 3.5 days, four did not abort but were resorbing them at from four to six days, two bore dead young at full term, one (ovariectomized at 14 days) retained four unusually large young (which evidently were too large to be born) until its death at 26 days of pregnancy, and one (ovariectomized at 13 days) gave birth to five viable young at 24 days of pregnancy. It is evident that the last two retained their young past the normal time for parturition.

By comparison with the uninjected controls (which aborted at an average of about 40 hours after ovariectomy) it is evident that the corpus luteum extract tended to maintain the pregnancy with varying success in all but four of these animals.

Two rats operated on at 18 days went to full term, but the living young of only one of these survived after 12 hours. A third rat aborted 1.5 days after ovariectomy.

Three rats operated on at 19 days went to full term, producing young which were nearly all alive. Another rat ovariectomized at 20.5 days bled

from the vagina 1.5 days later, when the young should have been born, and the young were born dead one day later.

The extract apparently was responsible for the functional mammary glands present in one female operated on at 13 days, in one at 18 days and in three at 19 days, since the controls ovariectomized before 21 days with one exception had no milk in their mammary glands.

Since in the two cases in which the extract was most successful in maintaining pregnancy (ovariectomized at 13 and 14 days, respectively) 0.4 cc. extract was injected daily distributed over a large subcutaneous area, it would seem evident that small doses and lack of distribution of the extract were responsible for insufficient absorption of the material to be effective in maintaining pregnancy in some of the other cases.

EFFECT OF OVARIECTOMY ON PREGNANCY IN GROUND SQUIRRELS

Double ovariectomy in varying stages of pregnancy in 12 female ground squirrels in 1927, in three in 1930 and in seven in 1931 resulted in termination of the pregnancy in each case, confirming the findings of Drips (5). However, only the abortion of a single embryo was seen. Animals frequently had blood on the opening of the vagina two to four days after the operation but no embryos were found on the paper used to cover the floor of the cages. While these observations would not preclude the possibility of abortion followed by the eating of the embryos, several cases of absorption of the dead embryos in the uterus of the animals which were opened up at various times after ovariectomy (see Fig. 1) gave evidence

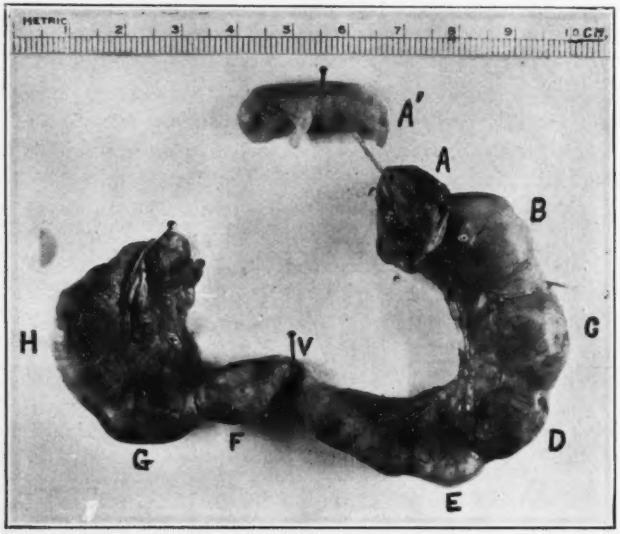

Figure 1. Uterus of an uninjected ground squirrel (No. 1219), 41 hours after double ovariectomy, showing resorption of the embryos, greater near the vagina (V) than near the tubal ends of the uterus. A', a normal but dead embryo removed from uterine enlargement A. B, enlargement with embryo, similar to A. C, enlargement with a smaller and more absorbed embryo. D, E, F, G, enlargements containing placentas and membranes but no embryos. H, enlargement with embryo half resorbed.

that abortion was not as common as resorption. The latter process, however, was not always accomplished successfully, with the result that the animal sometimes died with the putrid remains of the embryos, which had been normal at the time of ovariectomy, still in the uterus. As is seen in Figure 1, the absorption usually began near the vagina and progressed up each horn.

Unilateral ovariectomy in nine ground squirrels in varying stages of pregnancy resulted in continuance of the pregnancy, except for resorption in two cases, for which the poor condition of the animal could be held responsible since resorption was found also in one thin uncastrated animal. In most cases the maintenance of pregnancy by the remaining ovary was demonstrated by reopening the animal several days after the removal of one ovary, but two were allowed to go to full term and produced viable litters.

EFFECT OF CORPUS LUTEUM EXTRACT AND OVARIECTOMY IN PREGNANT GROUND SQUIRRELS

Since the ground squirrels were received from nature the stage of pregnancy could be only approximately determined from the size of the uterine enlargements. The length and width of the normal or larger swellings, each representing an embryo, were measured. It is interesting to note that one to four swellings smaller than the normal ones were seen often, indicating non-developing or resorbing embryos. Since the gestation period is 27 to 28 days (5, 6, 7) it is estimated that enlargements of 11x12, 15x15 and 20x15 mm. indicated pregnancies of about 19, 21 and 23 days' duration, respectively. Practically all of the ground squirrels in Table I were therefore in the last half of the gestation period.

An examination of Table I shows that while the extract did not delay death and subsequent absorption or abortion of the embryos in A3, A4, A11, and probably 1206, it appeared to be effective in maintaining pregnancy in the other 11 cases. Animals A14 and A15 went to practically full term but died from infection in the nose or the incision, carrying normal embryos of almost the normal size of full term. A12 went beyond full term, the embryos being heavier than the range of about 2-3 gm. for new-born young. No. 1203 bore five young and raised four of them, but a very small fragment of ovarian tissue was found in this animal. Nos. 1199, 1204 and 1211 evidently carried their young until near the time of normal parturition. As normal ground squirrels often eat their young as soon as they are born, the failure to find any young in two and the finding of partly eaten young in the third of the three animals mentioned does not indicate that the young were born dead as might be supposed from the fact that when young die they are eaten.

A careful examination of the ovariectomized ground squirrels at autopsy showed no ovarian tissue in the injected animals and also in the uninjected ones examined, except for a very small fragment found on a

TABLE I

Double Ovariectomy in Ground Squirrels with Injections of Corpus Luteum Extract

Animal Number	Enlargements of Uterus at Ovariectomy, mm.	Extract injected Daily, cc.	Bled at Days	Autopsy or Examination at Days	Enlargements in mm.; Other Observations at Autopsy or Examination	Degree of Effect*
1929 A0	Length Width 4 x 4	Ethyl 0.2	..	7 12	8x4.5 Embryos were badly degenerated.	++
1930 A3	11 x 10	Methyl 0.2	..	6	10x10; resorbing; no embryos seen in uterus.	—
A4	10 x 10	0.2	4	5	10x15; placentas and bloody masses resorbing; 1 had been aborted.	—
A11	15 x 15	0.2	3	4	10x9; 8x5; only placentas left; apparently had aborted.	—
A10	12 x 12	0.2	3	6	5 young born alive; recovered particle of ovary from coelom.	++
A12	13 x 12 and 15 x 13	0.2	..	10	35x15; average weight of 4 = 3.7 gm.; more than full term.	++
A15	20 x 15 (Resorbing in one horn of uterus)	0.3	..	3	25x18; weights, 2.1, 1.2, 1.6 gm., almost full term; animal died of infection in nose.	++
A14	20 x 15	Ethyl 0.4	..	5	30x15; 20x15; average weight of 8 = 2.3 gm.; 1 alive (2.6 gm.); others perfect but dead; about full term; adult died from infection.	++
1931 1199	10 x 12	0.4	..	7 10	Embryos very large; injections stopped. Shedding placentas.	++
1202	10 x 11	0.4	..	4	Accidentally choked; enlargements 21x14 mm.; embryos, 19x9 mm.; weighed 0.74 gm. each.	++
1203	11 x 12	0.8, 0.4 (6 times) 0.2 (4 times)	..	10	Bore 5 young, slightly oversized, lived; mammary glands functional; 1 small mature follicle found 3 weeks after parturition.	++
1204	11 x 13	0.4 (5 times) 0.2 (4 times)	..	9 10	Bore 3 young, normal size, partly eaten. 1 embryo and the placentas still in uterus.	++
1220	15 x 13	0.3 (once) 0.2 (3 times)	..	4	20x15; normal embryos; chewed open incision.	++
1216	15 x 14	0.4 (1 time) 0.2 (2 times)	1	1 3	Some blood on vulva. Embryos not felt; had been born or aborted.	—
1211	20 x 15	0.4 (3 times) 0.2 (1 time)	.. ..	3 4	Embryos large, clearly felt. Embryos gone; placenta seen on vulva; evidently young had been born and eaten.	++

* — No effect. + Some favorable effect. ++ Very favorable effect on maintenance of the pregnancy.

shred of mesovarium in No. A10. Histological examination of the region adjacent to the fallopian tube in Nos. 1202, 1204 and 1216 showed no ovarian tissue remaining in these animals at autopsy or after their young had been born, but one medium small follicle and a few very small atretic follicles were found in a very small mass of ovarian tissue recovered later in No. 1203.

DISCUSSION

The present work supports the view that the corpus luteum performs a function that is necessary throughout the period of pregnancy in most mammals, strengthening such conclusions by Corner and Allen (1, 2, 3) on the rabbit and by Harris and Pfiffner (4) on the rat. It also shows that the corpus luteum extract used is effective in maintaining the pregnancy in ground squirrels. The better success in the ground squirrels (which did not tend to develop hardened enlargements as did the rats, thereby showing better absorption) and in two rats at 13 and 14 days of gestation (which received larger doses) would indicate that doses of 0.3-0.4 cc. of the extract well distributed under the skin are more potent for these animals than smaller doses, especially if the material is not well distributed.

Since the uninjected ovariectomized rats apparently all aborted, but several of those which were injected were found absorbing their embryos in about four to six days after the operation, it would appear that the extract prevented abortion, probably by inhibition of uterine contractions, in these cases, but did not maintain the foetal nutrition adequately to keep the embryos alive, as death must have preceded absorption.

Delayed parturition occurred in two rats and in ground squirrel No. A12 and possibly in squirrel No. 1203, all of which had been injected. However, there were five injected rats in which parturition occurred at about the normal time, so this work neither verifies nor contradicts the conclusion of Harris and Pfiffner (4) that corpus luteum extracts delay parturition.

SUMMARY

Bilateral ovariectomy at different stages resulted in abortion in rats, except sometimes in late pregnancy, and in resorption in ground squirrels. Unilateral ovariectomy did not terminate the pregnancy. The daily injections of a bovine corpus luteum extract (0.2-0.4 cc.) after ovariectomy tended to maintain the pregnancy in a normal manner in the large majority of rats and ground squirrels toward the time of normal parturition.

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A CASE OF ADDISON'S DISEASE SUCCESSFULLY TREATED WITH CORTIN AND ADRENAL CORTEX EXTRACT

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Until recently no effective treatment for Addison's disease has been available. This disease, especially in its acute and subacute forms, leads to death in a few days and because of its rapid course there is very often no increase in pigmentation. Except for an occasional case recognized at operation, the subject nearly always comes to autopsy before diagnosis is made. Cases of Addison's disease very often show the symptoms of peritonitis and are found reported in the literature as pseudoperitonitis with acute insufficiency of the adrenals as, for instance, those reported by Mandel (7a).

REPORT OF A CASE

History: H. D., a female nurse, aged 40, entered the Medical Department on March 31, 1931, complaining of very severe pains in the abdomen and back. The onset of the pains was very sudden. Investigating the familial history we found that her parents and her sister died of tuberculosis. She had never been ill until December, 1930. At that time she had an attack of bronchitis and bronchopneumonia and was treated in our Department. From this time she complained of pains in the back.

The patient dated the onset of the symptoms about one month prior to her admission. She vomited, sometimes complained of pains in the back and the left side and had the sensation of a weight in the abdomen. She had no appetite and drank only tea with sugar. At the end of March she had the first attack of spastic pains in the abdomen accompanied by constipation.

Physical examination: The patient was moderately undernourished. The skin was pale. There was no pigmentation on the mucosa. The lungs and heart were normal. There was tenderness in the epigastric region and on the back above the kidneys. The pulse rate was 66. Systolic blood pressure was 110 mm. Hg and the diastolic pressure 60 mm. Hg. The total urinary output was very small (100—450 cc. in 24 hours). The albumen test was positive. The urine contained many white blood cells, few red blood cells, epithelia and bacteria. The gastric examination showed the total acidity to be 21 and free hydrochloric acid 11. The Wassermann reaction was negative. The blood culture and Widal test were negative. There was no blood found in the stools. The body temperature was 99.5°F.

Blood examination showed: Leukocytes, 4,800, of which 61 per cent were polymorphonuclear neutrophiles; 5 per cent eosinophiles; 32 per cent lymphocytes; 2 per cent monocytes. The blood sugar was 56 mgm. per cent measured according to the Crecelius-Seifert technic. The sedimentation time of the red blood cells was 17 hours, determined by the Faehreus' method. The basal metabolism was —25 per cent and no specific dynamic action was observed. The Pirquet test was positive. Ophthalmological examination showed nothing pathological. The blood pressure rose after an injection of one per cent adrenalin to 130 systolic pressure and 80 diastolic but no glycosuria appeared.

Roentgenographic findings: The pyelogram showed a small shadow in the calyx of the right kidney which was thought to be a concretion. The gastrointestinal system showed a few spastic contractions of the jejunum. There were no pathological findings in the skull, the lungs or the gall bladder.

Clinical course: Following admission to the hospital the patient became steadily worse. She became so weak that she could neither raise her head nor move her arms or legs. During the day she lay in a somnolent condition, not recognizing her friends. At night she complained of sleeplessness. She spoke very slowly and sometimes confusedly. It was remarkable that she could not distinguish distant objects, had diplopia and suffered from some visual hallucinations. She vomited frequently and because of her weakness had to be fed by a nurse, and she refused almost everything except tea. The systolic blood pressure fell to 85 mm. Hg and the diastolic pressure to 60 mm. Hg. The body temperature rose to 102.2°F.

On April 27 and May 1 and 2 she had chills and the temperature rose to over 103.1°F. The total urinary output for 24 hours was 100 cc. and acetone was found. On May 10 she complained of pain in the ear and in the otorhinolaryngological clinic the diagnosis of myringitis was made. In a short time some pigmentation appeared on the skin of the abdomen. She became emaciated and anaemic. The muscular power measured with the dynamometer fell to 4.

A diagnosis of acute insufficiency of the adrenals was made, called by some authors (Mandel, Averbeck and Neuresser) pseudoperitonitis with acute insufficiency of the adrenals. The diagnosis was verified by the results of the treatment.

The treatment was started as soon as the clinical and roentgenological examinations were completed. Injections of adrenalin caused undue cardiac reaction and injection of glucose increased the pains in the back over the kidneys. Therefore, we injected Hartman's Cortin because of its easy preparation and administration. We injected one cc. per day either deeply subcutaneously or intramuscularly. The injections were painful but did not cause any other symptoms. Alternately with Cortin we used an extract prepared by Štefl (16). This extract is prepared from the *whole adrenals.* From the dissected glands an extract with saturated cadmium chlorate solution in 96 per cent alcohol is prepared and purified with ether. The extract is a clear liquid and does not contain lipids. From our experiences with this extract we have concluded that it does contain the cortical hormone in a very concentrated form.

The effect appeared after one week. The condition of the patient improved. The systolic blood pressure rose to 110 mm. Hg and the diastolic remained the same. The pains, the vomiting, the visual and neurological disturbances disappeared and the patient regained her appetite. The daily urinary output rose to 700—1000 cc. and the albumen test became negative. The patient began to walk and gained 18 pounds in weight. The body temperature fell to 98.6°F and she recovered from the fever and chills. The muscular power rose to 18 during 12 days. Only a slight tenderness remained in the abdomen over the gallbladder. The blood sugar rose to 130 mgm. per cent but a slight anaemia appeared. The red blood cell count was 3,880,000; hemoglobin, 122 per cent; index, 1.60. After a new injection of one per cent adrenalin, the number of white blood cells rose during half an hour from 3,600 to 8,400 per c.mm. and the number of lymphocytes within 15 minutes from 19 to 41 per cent, but *no increase* in the blood pressure was observed.

The influence of the extracts was subjected to two tests. After the first eight injections the administration of the adrenal cortex extracts was interrupted. After one week all the former symptoms re-appeared but when the injections of the adrenal extracts were resumed, they disappeared after three days and after five days the patient could again walk. After a further series of injections we substituted distilled water for the adrenal extracts. Neither the patient nor anyone else noticed the change. After 12—18 days all the former complaints reappeared and then disappeared again upon the administration of adrenal cortex extract. By these two tests we ascertained the influence of Hartman's Cortin and the extract prepared by Štefl which were administered alternately. In the second experiment we excluded the possibility suggested by Ferreira de Mira (10, 9) who maintains the opinion derived from the experiments of Gorev with Ringers' solution that the effective substance of the adrenal cortex extracts is water, which removes the dehydration of the body and in this way almost all acute symptoms. This could not possibly be a factor in our case where such small amounts of liquid, namely one cc., were injected.

The patient has been kept alive by the administration of the adrenal cortex extracts for 6 months. She does not complain of any symptoms except sometimes of pains in the back and in the abdomen. She is able to make short trips without becoming tired. The treatment is being continued in the dispensary.

DISCUSSION

I should like to point out some peculiarities of our case. Especially interesting are the visual disturbances, as described above. Ophthalmological findings were negative. We still do not know anything about the cause of these disturbances but suppose that there is a reversible disorder of the nervus opticus, and for this reason I have called the complex of these symptoms "adynamia" of the vision.

Fever and chills are very seldom observed during the course of suprarenal insufficiency as reported by Mandel. They usually appear before a sudden increase of the temperature which can be produced either by the original disease, as for instance, tuberculosis, or as explained by Bayer (1), it is caused by a hyperthyroidie condition which very often accompanies the insufficiency of the adrenals.

The course of the urine output was very interesting. The total urinary output fell to 100 cc. and rose to 1000 cc. with improvement in the condition. It is possible to explain this phenomenon as due to the fact that the continuous vomiting caused a dehydration of the tissues and reduced the total urinary output. A similar observation, namely, an increased urine production, was observed by Swingle and Pfiffner (17) in epinephrectomized animals treated with cortical hormone.

From observations on our subject we have concluded that the terminal state of the acute insufficiency of the adrenals is at least the result of (a) dehydration, (b) hypoglycaemia and (c) disturbance in the acid-base equilibrium toward the acid side.

SUMMARY

A case report is given of a patient who was diagnosed as having an acute adrenal insufficiency. The diagnosis was verified by the successful treatment with Hartman's Cortin and an extract from the adrenal glands prepared by Štefl.

Thanks are due to Dr. J. Stefl for the preparation of the extracts which were all prepared in the Pharmacological Department of Masaryk University, Brno, Czechoslovakia.

ADDENDUM

Since the foregoing report was submitted for publication the patient has had one further acute attack from which she made full recovery. On March 1, 1932, she was on duty as a nurse in the hospital, receiving 1-1.5 cc. of cortical extract daily.

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POSTERIOR PITUITARY THERAPY IN DIABETES INSIPIDUS

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The writer has had the opportunity to observe closely an individual diagnosed as having idiopathic diabetes insipidus, with the following briefly summarized findings: The patient is a male, aged 22, without subjective complaints other than polydipsia and polyuria. The condition appeared suddenly at 5 years of age, without known injury or antecedent illness. There is no familial record of the disease. Physical examination reveals no abnormality excepting a resting blood pressure of 100/65 mm. Hg. Basal metabolic records are well within normal limits. The sella turcica gives no suggestion of abnormality in x-ray negatives. There is no suggestion of hemianopsia. The eye grounds evidence no abnormality. The blood contains cellular elements in normal proportion. The following chemical findings were obtained on analysis of the blood:

Blood sugar (fasting)	104 mgm./100 cc.
Blood Urea	12 mgm./100 cc.
Non-protein nitrogen	28 mgm./100 cc.
Blood chlorides	550 mgm./100 cc.

The urinary excretion averages 10 liters in 24 hours, with specific gravity of 1.001 to 1.002, almost colorless, giving negative reactions to tests for sugar, indican, protein and acetone. The quantitative urinary constituents are shown in Table No. 1, giving comparative findings before and after treatment. Although the chloride content is not markedly out of the ordinary, it would tend to correspond with the findings of Stehle (1), who claims that the diuresis is due to a disturbance of salt metabolism.

A study of kidney function shows that in spite of the polyuria the day to night ratio of quantitative urine secretion is as 2:1. There is, however, a definite impairment of the concentrating power of the kidney. By voluntary restraint, involving much discomfort, the patient went for a period of eight hours with fluid intake limited to 210 cc. The urinary output during this time amounted to 3,100 cc., equalling the average excretion with unrestricted intake of fluid. This experience agrees with the viewpoint that polydipsia is the result of polyuria, in an attempt by the body to replenish the water loss. This is not in agreement with the understanding of Curtis (2). The restricting of fluids to patients with diabetes insipidus entails considerable suffering.

The carbohydrate tolerance test in this patient shows a normal curve with a normal renal threshold for sugar. The work of Gibson and Magers (3) tends to show that cases of this type usually have a sugar tolerance curve resembling that obtained in diabetes mellitus. The difference in sugar tolerance curves in this condition may well be due to whether or not the cause of the disease may be a lesion in the mid-brain.

The literature concerning diabetes insipidus indicates the trial of a large number of therapeutic agents. Preparations of the posterior pituitary have been the most serviceable. Hypodermic injection of extracts of this tissue have been most commonly used. The relief of polydipsia and polyuria is usually marked, though of short duration. The injections are painful, placing quite a handicap upon this method of administration. Motzfeldt (4) in 1917 and Rees and Olmsted (5) in 1922 claimed good results with oral administration of enteric preparations of desiccated posterior-pituitary of the ox. Tablets of this product with heavy salol coating were given this patient in amounts of 30 milligrams every six hours A reduction in urinary output occurred, from ten liters to seven liters, in 24 hours. The change was far from satisfactory and expensive when considered as a constant therapy. Capsules containing barium sulphate were seen apparently floating on the surface of fluid near the cardia for periods of several hours. This was verified on repeated observations and may partly explain the poor results with this method of administration. During the eight-hour restriction in water intake the stomach appeared empty on fluoroscopic observation and the capsules passed through the pylorus shortly after swallowing.

A supply of fresh pituitary tissue was obtained and desiccated. The patient volunteered to assist in pulverizing the posterior portion of the pituitary tissue. He was impressed with a remarkable freedom from thirst and frequency of urination for six hours following the trituration of the material. This relief suggested the value of nasal insufflation of the powder. Blumgart (6) in 1922 reported beneficial results from this form of administration, which has since been verified by others.

A physician limiting his practice to diseases of the nose and throat carefully examined the nasal mucosa of the patient in order that he might determine any local change occasioned by the frequently repeated deposit of dried posterior-pituitary substance upon the mucous membrane. Following continued use of this form of administration for one year, no visible change has occurred in the nasal mucosa. No subjective symptoms of irritation or other change has been noticed by the patient.

Application was made by means of a powder blower for a time, using approximately 10 mgm. per dose. There was some waste in powder that would escape with following expirations and some that passed into the pharynx. Equally satisfactory results were obtained by the application of not more than 5 mgm. of the powder to the nasal mucosa by means of the finger tip, once in 8 to 10 hours. Table I indicates the change in urinary constituents following the use of the desiccated posterior-pituitary tissue.

TABLE I

URINARY CONSTITUENTS IN DIABETES INSIPIDUS

	Preceding Therapy:	During Use of Desiccated Pituitary:
24 Hour Quantity	10,000 cc.	1,500 cc.
Color	Colorless	Amber.
Specific Gravity	1.001 to 1.002	1.018 to 1.020.
Albumin	Negative	Negative.
Sugar	Negative	Negative.
Acetone	Negative	Negative.
Indican	Negative	Negative.
Blood	Negative	Negative.
Total Solids	50 grams/24 hours	52 grams/24 hours.
Total Nitrogen	8.04 grams	8.19 grams.
NH_2 Nitrogen	0.72 grams	0.74 grams.
Urea Nitrogen	6.85 grams	6.96 grams.
Sodium Chloride	15.8 grams	11.6 grams.
Total Acidity	144 cc. N/10 NaOH	140 cc. N/10 NaOH.

The only contrast in chemical constituents in 24-hour quantities of urine consisted in a slight reduction in chloride excretion. This, in a measure, tends to support Stehle's (1) idea of the condition being caused by an imbalance in the salt metabolism, holding that the anti-diuretic effect of the posterior pituitary is probably due to an increased capacity of the tissues to hold water.

The blood showed no chemical changes following pituitary therapy with the exception of a slight lowering of the chloride content. There was no change in the functional activity of the intestines with use of sufficient pituitary powder to afford complete relief of the polydipsia and polyuria. Blood pressure measurements at 15-minute intervals following application of the pituitary powder were within limits of normal variation, not increasing over 5 mm. of mercury over a period of three hours. The blood pressure following one year of use of the pituitary powder remains at the level existing before instituting this therapy, 100/65 mm. Hg.

A decided change has occurred in subjective symptoms, from constant lassitude to a feeling of well being and reserve energy, independent of the lack of change in blood pressure. There was never any psychotic manifestations in the patient as far as he can remember. The patient never spent much time reflecting on the condition until six months before the therapy was started. At the age of four years the patient was restless and irritable over a period of two years. The onset of diabetes insipidus was coincident with the onset of the irritableness. There was never any convulsion, fever, or any other evidence of organic cerebral disease. The diabetes insipidus in this case did not give rise to any psychiatric disturbance. There was no evident organic lesion to give rise to any organic psychoses, and the knowledge that the symptoms could be controlled stopped any possible functional psychoses which might have come on in later life. However, there was a decided mental relief in the knowledge that the condition could be controlled. In the year or so in which the therapy has been under way, there has been an improvement in general health, but there has been no change in general behavior, mental acuity, emotional reactions, or mental activity other than an increased desire to carry on his work.

Pituitary extract incorporated in a vegetable jelly, kindly supplied by one of the manufacturing houses, was used in place of the powder for a

time, by nasal application. Apart from a failure to give relief from the polydipsia and polyuria in equal degree to that afforded by the powder, the patient found the jelly less agreeable in the nose. The powder would be less expensive than the jelly by a considerable margin.

SUMMARY AND CONCLUSIONS

1. Prolonged study in a single subject indicates that desiccated posterior pituitary in powder form applied to the nasal mucosa gives very satisfactory relief from the symptoms of diabetes insipidus.

2. The urinary secretion, qualitatively and quantitatively, returns to normal figures.

3. The nasal mucosa is not damaged by the local application of powdered pituitary substance in sufficient quantity to afford complete relief from the symptoms of the disease.

4. The quantity of pituitary substance necessary to afford complete relief is less, in powder form, than the amount required by hypodermic injection of an extract or nasal application of an extract in jelly base, judging by the results obtained in the individual herein reported upon.

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EPILEPTOID ATTACKS AND HYPERINSULINISM

THE REPORT OF A CASE

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The following case report is an attempt to depict briefly the symptoms, findings, treatment and progress of a male patient suffering from hyperinsulinism who was under constant observation for a period of several years. The basis for the diagnosis of hyperinsulinism is contained chiefly in the following facts: Attacks of amnesia and coma occurring usually in the forenoon, the finding of a very low blood sugar during the individual attacks, the freedom from amnesia and coma during periods in which frequent carbohydrate feedings were given, and the failure to find any other cause which could be positively associated with the illness.

History: The patient entered the Union Printers' Home, Colorado Springs, Colorado, May 16, 1926, at the age of 44 years.

Family History: The family history seemed irrelevant to the patient's illness, and it is, therefore, not repeated.

Past History: The patient had for some years previous coughed up a great deal of purulent sputum. He also had experienced frequent attacks of rhinitis, and complained of a more or less continuous purulent discharge from the nose.

During 1917 he received a kick from a horse which had broken his lower jaw; his recovery from this injury was apparently without complications or residual impairment.

History of the Present Complaint: The onset of the present trouble was in 1920 when he began to experience attacks of amnesia and unconsciousness; these attacks usually began in the forenoon, and while their number in a given time varied somewhat, he often had several in a single week. While in the grip of an attack, he would usually lie down or even fall down, although he sometimes walked about muttering or shouting; during the more severe phases, he frequently exhibited moderate tonic or clonic muscular spasms and stertorous breathing. When he regained consciousness, he rarely or never had any recollection of what had occurred, but before unconsciousness overcame him, often felt a warning aura in the form of dizziness, chilly sensations, weakness, diplopia, perspiration and a craving for sweets. He early became aware of the fact that an attack could frequently be aborted by eating something or drinking brandy.

Shortly before his admission to the Union Printers' Home, he was observed by Dr. C. F. Kemper, Denver, Colorado, who noticed the similarity of the symptoms to those produced by an overdose of insulin, and on examining the blood, found the sugar content low. A tentative diagnosis of Addison's disease was made. Under frequent carbohydrate feeding he remained free from the trouble; however, after a short time he abandoned the treatment and promptly lapsed into his former condition.

During September, 1928, a diagnosis of "epileptic equivalent" was made at the Mayo Clinic. No evidence of Addison's disease was found. It could not be determined whether or not the trouble was caused by the kick from the horse which the patient had received in 1917. He was advised to try bromides whenever he felt an attack impending.

During the latter part of September, 1928, the patient entered the Hospital of the University of Colorado, under the service of Dr. F. G. Ebaugh.

Here the Wassermann reaction of the blood was found to be negative; the basal metabolism was reported to be within normal limits; the sugar content of the blood was 64 mgm.; the non-protein nitrogen of the blood, 30 mgm.; and the urea content 20 mgm. per 100 cc. Nothing abnormal was found in the urine. The spinal fluid was examined on two different days. The first examination

showed a cell count of 4 per cubic millimeter, a negative Wassermann reaction, a protein content of 25 milligrams per 100 cc., a sugar content of 28 milligrams per 100 cc., and a negative gold curve reaction. The second examination revealed similar findings except that the protein content was 30 and the cell count was 6. Ventriculography disclosed nothing of a definitely pathological nature. The sugar tolerance curve showed prolongation and lowering. No diagnosis was made.

During observation at the Union Printers' Home, the patient had always been well-nourished and muscular; his weight varied from about 175 to 188 pounds; his height was 5 feet, 10½ inches.

Inspection of the face showed some brownish pigmentation about the forehead and sides of the neck, the distribution of which suggested a pituitary rather than an adrenal origin.

The chest examination revealed impaired resonance and narrowing of Kroenig's isthmus over the right apex; a few rhonchi were heard over the same region. Examination of the heart disclosed no significant abnormality. His blood pressure varied from 92/60 to 126/76 during the several years of observation.

Laboratory Investigation: During May, 1926, tubercle bacilli were found once in his sputum; but subsequently repeated examinations failed to disclose the bacilli again. The leucocyte count varied from 14,000 to 18,000 white cells per cubic millimeter, while the erythrocyte count was usually 5,000,000 per cubic millimeter, and the hemoglobin was 96 per cent by the Dare method.

Roentgen Ray Investigations: In April, 1927, a skiagram of the skull revealed no abnormality. A chest plate in December, 1927, disclosed a hazy righ apex; the root shadows on both sides were increased in density, and the left side showed many adhesions to the diaphragm. Both antrum and ethmoid regions were clouded.

During March, 1928, Roentgen ray pictures taken after the administration of iodine contrast dye demonstrated a normal gall bladder shadow which disappeared one and one-half hours after taking a fat meal.

On May 10, 1928, while the patient was in coma, blood was taken from his arm vein and the sugar content was found to be 30 mgm. per cent. Several times later this procedure was repeated, when the patient was in coma, with similar results. However, when the patient was not in coma, the sugar content of the blood varied from 64 to 76 mgm. per cent.

The reaction to insulin was then tested. Successive daily doses of 5, 10, 15 and 20 units were ineffective in precipitating an attack. The blood sugar before the last dose was 66.6 mgm. per cent, and 20 minutes later was 50 mgm.

Diagnosis: On April 19, 1928, a tentative diagnosis of hyperinsulinism was made. The possibility was recognized that this could be relative or secondary to some other imbalance as well as due to adenoma, hyperplasia, neoplasm or overactivity of the pancreas.

The Peterman ketogenic diet was given a trial on several different occasions, but it did not control the attacks; in fact, urine was taken on one or two occasions while the patient was in coma and considerable amounts of acetone were found.

The Mayo Clinic advised the trial of bromides to control the attacks. Luminal, bromides and other sedatives were given many trials but the results were always negative.

Dr. C. F. Kemper prescribed the Moorehead regimen. This, too, failed to influence the attacks, as did also the regular administration of pituitrin. Pituitrin was of some aid in restoring consciousness when the patient was in coma; but for this purpose, adrenalin was much superior, as was also the intravenous administration of glucose. Adrenalin and glucose given simultaneously caused a still more prompt return to consciousness.

January 29, 1930, frequent carbohydrate feedings were resumed once each hour during the forenoons. Up to July 8, 1931, the patient had suffered no attacks of amnesia or coma.

DISCUSSION

The facts that this patient remained muscular and overweight; had never manifested any serious gastrointestinal disturbance; had no known gastrointestinal intolerance for fats; was not exhausted in the evening after

being up and about all day; and, instead of growing progressively worse, has seemed rather to improve, appears to exclude Addison's disease.

The significance of his negative reactions to increasing doses of insulin is rather difficult to evaluate, but the tests were made in the evening; they were not continued to the point of producing shock. His attacks of amnesia and coma occurred periodically, and it is to be presumed that during these crises the insulin content of his blood was largely above normal.

It seems unlikely that the head injury received in 1917 was a direct cause of the amnesia and coma, because of the time intervening between the injury and the first appearance of the trouble in 1920. That it could be an indirect cause by affecting some vegetative center of the brain is possible, but too little is known concerning such an association to make it safe to venture an opinion.

And, lastly, the negative effect of sedatives such as luminal or bromides, the failure of the ketogenic diet to control the attacks, the finding of an extremely low blood sugar content during the attacks, and the prompt and favorable response to carbohydrate feeding would seem to remove "idiopathic epilepsy" from the realm of possibilities.

SUMMARY

A patient exhibiting symptoms of hyperinsulinism was closely observed over a period of several years. The chief indications of the disorder were frequent attacks of amnesia and coma which occurred usually in the forenoon and which were often accompanied by convulsions, and during which the blood sugar content fell to 30 mgm. per cent.

Treatment such as luminal, bromides and other sedatives, as well as the Peterman ketogenic diet, failed to prevent the attacks, hence epilepsy is excluded as the etiologic factor. Pituitrin promptly restored consciousness during the individual attacks, but for this purpose adrenalin plus glucose given intravenously gave best results. Carbohydrate given every hour during the forenoon has kept the patient free from attacks for about a year and a half.

Book Reviews

THE VITAMINS. H. C. Sherman and S. L. Smith. 2nd Ed., 1931. The Chemical Catalog Company, Inc., New York.

The second edition of Sherman and Smith's book on the vitamins brings up to about the middle of 1930 a comprehensive summary of our rapidly increasing knowledge in this field of nutrition. There is comparatively little in the book of direct endocrine interest, but endocrine articles with significant bearings on vitamin problems have been summarized, or listed in the very complete bibliography.

Abstract Department

Culpability of the suprarenals in the symptoms and late death from extensive superficial burns. Berkow, S. G., M. J. & Rec. **184**: 386. 1931.

Late death from extensive burns is described as that in which the end comes suddenly after ten days to three weeks of apparently successful progress. This abrupt death is more often seen in children. Evidence of suprarenal deficiency in extensive burns, detailed in the article, consists of (1) suprarenal pathology constantly found at autopsy; (2) similarity between the distinctive signs and symptoms, including the manner of death, following experimental adrenalectomy and after extensive superficial burns; (3) clinical evidence. The impression gained from actual experience with suprarenal therapy in 19 cases supplemented the theoretical grounds upon which this therapy was founded. The administration of suprarenal medullary extract in extensive burns is worthy of clinical trial.—Author's Abst.

The depletion of muscle sugar by adrenalin. I. Bischoff, F. and M. Louisa Long, J. Biol. Chem. **87**: 47. 1930.

Fifteen fasting rabbits were given 0.25 mgm. adrenalin per kgm. subcutaneously and sacrificed at varying time intervals, blood sugar and muscle sugar (reducint) analyses being made. Five control litter mates were sacrificed to establish the resting muscle sugar level. A comparison of 4 muscle sugar methods was made upon various samples. While there was an appreciable difference in the absolute values by different methods, the relative differences were consistent throughout the series. The blood sugar and muscle sugar values did not run parallel after the subcutaneous administration of 0.25 mgm. of adrenalin per kgm. From the 8th to the 24th hour the muscle sugar was at a very low level. At the 3rd hour the muscle sugar had already fallen to the fasting value, while the blood sugar was at the peak of the curve. The in vitro experiments of Sahyun and Alsberg, which indicated that deglycogenated whole skeletal muscle has the power of utilizing glucose in vitro, are invalidated by the above observations.—Authors' Abst.

Effect of continuous intravenous injection of epinephrine on the carbohydrate metabolism, basal metabolism and vascular system of normal men. Cori, C. F. and K. W. Buchwald, Am. J. Physiol. **95**: 71. 1930.

Epinephrine was injected intravenously into normal men for a period of 30 minutes; 0.00005 mgm. per kilo per minute proved to be the lowest rate of injection which still caused a rise in blood pressure, blood lactic acid and basal metabolism; 0.000025 mgm. per kilo per minute was still able to increase pulse rate, respiration and blood sugar. After the epinephrine administration pulse rate, respiration and blood pressure returned to the original level in 5 to 10 minutes, basal metabolism in 15 to 30 minutes, while generally more than 30 minutes were required for blood sugar and blood lactic acid.—Authors' Summary.

Red blood cells and the absorption of certain nutritional and hormonal substances, especially adrenin (Les hématies et l'absorption de certaines substances nutritives et hormonales, spécialement de l'adrénaline). Gedroyc, M. and W. Koskowski, Compt. rend. Soc. de biol. **105**: 409. 1930.

Among other substances adrenin was studied. Red cells allowed to stand in an adrenin solution centrifuged and later hemolized, raised the blood pressure markedly when injected into dogs. If the adrenals of dogs were stimulated and their red cells tested physiologically, adrenin was present while it could not be detected in the red cells of controls whose adrenals had not been excited.—J. C. D.

On the nature of the chromaffin reaction (Sur la nature de la réaction chromaffine). Gerard, P., R. Cordier and L. Lison, Compt. rend. Soc. de biol. **105**: 876. 1930.

This gives further evidence that the Henle or chromaffin reaction for adrenin is due to an oxidation of part of the adrenin from a dioxphenyl to a quinone compound with a reaction between these two.—J. C. D.

The Coffey-Humber extract of suprarenal cortex substance: A clinical study of four hundred and fifteen patients with malignant tumors who received experimental injections. Harris, R. H., J. A. M. A. **97**: 1457. 1931. Abst., A. M. A.

The author gives a brief summary of the results of a clinical and pathologic study conducted by the W. K. Kellogg Foundation. Four hundred and fifteen persons who had carcinoma or sarcoma were given subcutaneous injections of suprarenal cortex substance extract by representatives of Drs. Walter B. Coffey and John D. Humber, and were observed and examined by physicians of the foundation. Case abstracts made by former physicians were furnished by these patients on beginning experimental injections. The majority of the patients first had received injections of the extract at the Los Angeles Central Coffey-Humber Clinic and were transferred with their records to the Kellogg Foundation. Some patients were accepted by the foundation for their first injections of the extract. The majority of the patients were ambulatory. They received injections of the extract and made progress reports at the foundation clinic. They lived in widely separated localities and were encouraged to depend on cooperating local physicians for general medical care and on surgeons of their choice for the performance of such palliative operations as might become necessary. Approximately seventy patients in all were brought to the clinic by automobile or ambulance and received the extract injections without entering the building. One hundred and eighteen patients received extract injections and were under the care of physicians of the foundation for varying periods of time at a hospital, which was leased and operated by the foundation exclusively for this purpose. Some who received the extract were first ambulatory, then car patients and finally hospital patients. With few exceptions, the patients whose cases are reported were incurable by surgical operation, by radiation therapy or by any other known method of treatment. The diagnosis of malignancy was established by microscopic examination of tissues in 326 cases, and by roentgen examination or exploratory surgical operation in other cases. A few patients had had apparently complete surgical removal of malignant tumors and had no discoverable metastases but were permitted to receive injections of the extract as a prophylactic measure. The study of such patients could be useful in determining the effect of the extract in the prevention of recurrence only if there should be no recurrence in an unusually large percentage of these patients after continuing use of the extract over a period of several years. The author gives the following summary of the results of a statistical study of his observations: (1) The benefits of use of the suprarenal cortex extract experienced by patients with malignant tumors in relation to gain in weight and relief from pain did not occur uniformly or in the majority of the patients observed. (2) The extract administered to these patients had no selective influence on the growth, necrosis or sloughing of malignant tumors. (3) Necrosis and sloughing of malignant tumors were not beneficial but were detrimental to these patients, producing hemorrhage, anemia, distressing fistulas, perforation with abscess or peritonitis, and other serious consequences. (4) Cure of malignant disease in patients with advanced carcinoma or sarcoma, in view of the experience of the patients of this series, cannot reasonably be expected to occur as a result of use of the suprarenal cortex extract. (5) The benefits to be expected from use of the suprarenal cortex extract lie principally in improved appetite, improved muscle tone and bettered feeling of general well being of patients who are ambulatory or who are not too far advanced toward a fatal termination of the disease.

The relation of cortin to the maintenance of body temperature. Hartman, F. A., Katharine A. Brownell and A. A. Crosby, Am. J. Physiol. **98**: 674. 1931.

A study has been made of adrenalectomized rats exposed to cold after the injection of cortin, adrenalin chloride and isotonic NaCl solution. Animals which resist cold well show considerable voluntary movement, while those

which do not are very quiet. Normal rats show a fall in colonic temperature of a little more than 1°C. when exposed to cold (4-18°C.) for several hours. Cortin-treated adrenalectomized rats show a drop of 2° to 3°C., while NaCl-treated adrenalectomized rats show a fall of 12°C. or more and many die. Injected adrenalin did not increase the resistance of adrenalectomized rats. The metabolism of rats is lowered 10 to 20 per cent by adrenalectomy but returns to normal when an adequate supply of cortin is furnished. The fall in temperature of adrenalectomized rats when exposed to cold is due to a decrease in heat production. Although the latter increases at first it falls far short of making up for the heat loss and later goes below that of normal rats at 28°C. The administration of cortin enables such animals to produce heat almost as well as normals. The ability of cortical extracts to protect adrenalectomized rats against cold has been used as a test for potency. There is an increase in the weight of the adrenals of normal rats exposed to cold for 20 hours or longer.—Authors' Summary.

Action of adrenalin on the red blood picture (Über die Wirkung des Adrenalins auf das rote Blutbild). Istanamowa, T. and Chudoroschewa, Ztschr. f. d. ges. exper. Med. **71**: 212. 1930. Abst., Chem. Absts. **25**: 4614.

The intravenous injection of adrenalin into rabbits usually resulted in an increase in reticulocytes along with a rise in erythrocytes and hemoglobin. The increase was due to bone marrow stimulation and also to the effect of adrenalin on the vessels of the bone marrow.

The secondary rise in blood pressure following peripheral splanchnic nerve stimulation. Johnson, V. and Adelaide Johnson, Am. J. Physiol. **99**: 160. 1931.

When the adrenal glands are intact and the medulla functional, the blood pressure curve resulting from peripheral splanchnic nerve stimulation consists of a sharp rise, a "step," and then a secondary rise, with a subsequent return to the pre-stimulation level. The secondary rise in this case is due partly to the secretion of adrenalin. When the adrenals have been removed the secondary rise is not abolished, but occurs in modified form. This residual secondary rise, entirely independent of the adrenal glands, is not due to contraction of the spleen, liberation of pressor or cardio-accelerator substances from the liver, and probably not to increased cardiac output or vaso-motor reflexes. It is believed to be a peripheral phenomenon involving a splanchnic nerve-end organ mechanism. This end organ may be chromaffine tissue liberating an adrenalin-like substance, or some other tissue, possibly the blood vessel musculature, elaborating a pressor substance. Or it may be rhythmically contracting vascular musculature.—V. Johnson.

Determination of the area for irradiation of the adrenal gland (Determination de champ d'irradiation des glandes surrenales). Lucien, M. and M. Bleicher, Compt. rend. Soc. de biol. **106**: 206. 1931.

Formalin fixed bodies with adrenals rendered opaque to the x-ray were photographed and the best area to reach the gland determined. The area outlined by the directions below is such that it will include a large part of the adrenal in spite of individual variations and those between the right and left side. Two lines are drawn laterally at right angles to the vertebral line, one from the middle of the dorsal spine of the first lumbar vertebra and one from the upper edge of the spine of the eleventh thoracic. Two lines, one along the vertebral line and one 4 inches lateral and parallel with it complete the rectangle.—J. C. D.

The relations between the cortical and medullary portion of the adrenals in mammals (Sur les rapports entre la substance corticale et la substance médullaire de la surrénale des Mammifères). da Costa, A. C., Compt. rend. Soc. de biol. **105**: 141. 1930.

This is a brief note reviewing some of the evidence against the idea that the cortex may at times secrete adrenin.—J. C. D.

Should the carotid body be classed as a paraganglion (Peut-on classer le ganglion carotidien parmi les paraganglions)? Milcou, S. M., Compt. rend. Soc. de biol. **105**: 55. 1930.

In man, monkeys, horses, dogs, cats, rabbits, rats, cattle and frogs, the carotid body failed to take the stain when exposed to the salts of chromic acid. Extracts of the body in 16 out of 22 cases failed to give the Ehrmann-Meltzer pupillary reaction for adrenin. The type of cell in the carotid body, as measured, is very different from that found in the abdominal paraganglia. All these points are against the carotid body being one of the paraganglia.—J. C. D.

Effect of an extract from the adrenal cortex on the survival of decapsulated guinea pigs (Action d'un extrait cortico-surrénal sur la survie du Cobaye décapsulé). deMira, F., J. Fontes and K. Jacobsohn, Compt. rend. Soc. de biol. **105**: 146. 1930.

In nine animals the extract prepared as outlined by Swingle and Pfiffner and administered immediately after operation failed to prolong life.—J. C. D.

Experimental justification for the functional relation of the adrenal cortex to the sex organs (Experimentelle Begrundung der Functionellen Beziehung der Nebennierenrinde zu den Geschlechtsorganen). Müller, C., Klin. Wchnschr. **9**: 1967. 1930.

Fresh adrenal glands from cattle were obtained from the slaughter house and a portein-free extract of the cortex made. Every other day 0.5 cc. of this extract was injected subcutaneously into 5 normal young female white rats and also into the same number of thymectomized female rats. After several weeks treatment all of the animals showed great hypoplasia of the uterus horns and poorly developed uteri with little surrounding fat tissue. The vaginal canals opened very late. Unfortunately the age of the rats at which the treatment was begun and the time of the opening of the introitus vaginae are not given.—L. B. Nice.

Studies on the function of the adrenal cortex. III. Adrenal cortex and cholesterol metabolism (Studien über die Funktion der Nebennierenrinde. III. Nebennierenrinde und Cholesterinstoffwechsel). Reiss, M., Endokrinologie, **7**: 1. 1930.

Continuing his studies on the function of the adrenal cortex, the author tests the effects of his beef adrenal cortex extract on cholesterol metabolism. Administration of the extract intravenously, intramuscularly and even per os to normal rabbits brought about a decrease in blood cholesterol within a few hours. Prolonged treatment resulted in increased total body cholesterol in mice. The author believes that these two reactions indicate cholesterol-fixing properties of the extract, in which the reticulo-endothelial system is involved, because a previous injection of India ink will interfere with the action of the extract on cholesterol.—R. L. Zwemer.

Clinical investigations into the effect of intravenous injection of insulin. V. The action of adrenalin upon the stomach secretion. Roholm, K., Acta med. Scandinav. **74**: 359. 1931.

From the supposition that the stimulation of the gastric secretion brought on by insulin might be due to an adrenalin effect, experiments are made on the effect of adrenalin upon the fasting secretion of the stomach. In 10 experiments, no change could be demonstrated in the fasting secretion after administration of adrenalin (1 mgm. subcutaneously). The findings indicate that Okada and co-workers' hypothesis of a humoroneural regulation mechanism for the secretion of the digestive glands is not tenable, at any rate as far as the stomach is concerned.—Author's Summary.

Treatment of Addison's disease with cortical hormone of suprarenal gland. Rowntree, L. G., C. H. Greene, R. G. Ball, W. W. Swingle and J. J. Pfiffner, J. A. M. A. **97**: 1446. 1931. Abst., A. M. A.

The authors state that the clinical changes detected in observation of patients with Addison's disease who respond satisfactorily to treatment with

the cortical hormone of the suprarenal are: (1) disappearance of anorexia, nausea and vomiting, and reappearance of appetite and development of the sense of hunger; (2) relief from fatigue and increase in strength and endurance; (3) disappearance of pain, and improvement in sleep; (4) decrease in pigmentation; (5) gain in weight; (6) return of normal gastro-intestinal activity; (7) change in the mental attitude characterized by hope and euphoria; (8) moderate increase in blood pressure when the patient is in crisis or shock but very little change when the patient is in good condition; (9) increased resistance to infection or to the effects of surgical procedure, and (10) partial or complete rehabilitation of the patient and return to work. The most constant and striking effect is the disappearance of anorexia, nausea and vomiting, and also of the distressing pain in the loins that is present in so many of these patients. Increase in strength and endurance appears early, is marked, and is out of all proportion to the objective observations. The decrease in pigmentation becomes apparent within three or four days. A new problem is in the offing. With other methods of treatment the patients have been content to remain invalids, but the physical and mental improvement following the administration of the cortical hormone has led, in many instances, to the requests to return to work. Because of the inadequate supply of the hormone and also because of lack of knowledge as to the permanence of the effect, these requests have been denied thus far. In one instance the authors observed a patient under treatment with the cortical hormone pass through an infection which they have every reason to believe would have been immediately fatal in the absence of treatment. A tooth was removed without difficulty from one of their patients. This will bring to the fore the question of surgical procedure in Addison's disease for the removal of diseased glands. Surgical removal of a diseased suprarenal gland has been performed but once in the history of medicine. Idiosyncrasies to drugs constitute a serious clinical problem in Addison's disease. In the old days, if a patient was given a purgative he might go into collapse and die. The administration of almost any drug was attended with uncertainty as to its action. Once the patient is under the influence of the cortical hormone, the authors are of the opinion that the response to drugs will be much more normal than has been true in times past. The gain in weight of 13 of the patients treated by them is indicated in a table. The majority of the patients gained weight, and some did so in a very striking manner. Three gained 10 pounds (4.5 kgm.) or more in the course of a month. Associated with the gain in weight there was a corresponding shift in the nitrogen balance with nitrogen retention.

Studies in experimental scurvy. X. On the adrenalin content in suprarenals and the amount of the adrenalin-like substance in the serum of guinea pigs fed on a Vitamin C free diet. Shinsuke, O., J. Biochem. **12:** 419. 1930.

Adrenalin in suprarenals (Suto-Inoue method) and adrenalin-like substance in serum (Chikano method) were determined in normal, fasting (up to 6 days) and scorbutic (Sherman diet for up to 22 days) guinea pigs. The total content of adrenalin in the suprarenals fell from 0.0585 mgm. (average for normal group) to 0.0225 mgm. (average for scorbutic group) in 17-22 days of Sherman diet. The fasting group averaged 0.0358 mgm. The adrenalin-like substance in serum also decreased in both scorbutic and fasting groups, but not to as great an extent as the adrenalin in the suprarenals. Normal group 14.6 mgm.%, scorbutic group 8 to 11 mgm.%, fasting group, 8 mgm.%. The authors conclude that the decrease, both in adrenalin and the adrenalin-like substance, is not entirely the result of inanition.—B. S. Walker.

Primary hypertension in childhood: The influence of hyperadrenalism. Siegel, A. E. and P. C. Thomas, Am. J. Dis. Child. **41:** 728. 1931.

A 12-year-old girl who was overweight and overheight showed a persistent blood pressure of 130 mgm. of mercury without any demonstrable cause. The injection of 1 cc. of 1-1000 solution of epinephrine was followed by a rise in blood sugar from 95 mgm. per 100 cc. to 172 mgm. in 30 minutes and 182 mgm. in 60 minutes, with a gradual fall to 132 mgm. in 2 hours. A similar injection caused an early depressant effect on the blood pressure and a later elevation. The basal metabolic rate was minus 18. The authors consider that the persistent hypertension in this patient was due to hyperadrenalism because of the effects of the epinephrine injections.—M. B. G.

The vaso-sensory nerves and adrenin secretion (Nerfs vasosensibles et adrénalino-sécrétion). Tournade, A. and J. Malméjac, Compt. rend. Soc. de biol. **106**: 444. 1931.

Injection into the femoral artery of dogs of an appropriate stimulant to the vasomotor nervous system results in a definite discharge of adrenin as indicated by a contraction of the spleen. This is the reverse of the inhibitory effects following stimulation of the vagus.—J. C. D.

The effects of hyperhormonization with follicular liquids on hypophysis, thyroid and suprarenals (Sugli effetti che la iperormonizzazione con liquido follicolare determina nella ipofisi, tiroide e capsule surrenali). Bisceglie, V., Endocrinol. e patol. costit. **5**: 70. 1930. Abst., Am. J. Obst. & Gynec. **22**: 657.

The results obtained with the administration of follicular liquid are: (1) Hypophysis (anterior lobe) modifications are seen which augment in intensity parallel to the follicular liquid administration. These modifications consist in hyperemia with a constant increase of the acidophilic, disappearance of the basophilic cells and some increase of colloid. (2) There is a gradual reduction of the volume of the thyroid cells, showing a smaller quantity of colloid, and a notable hyperplasia of the intercellular epithelium. (3) With short treatment no defined changes are seen in the suprarenal cortex. With longer administration of the liquid, there is a slight hyperemia, changes in the spongy tissue in the zona reticulata and fasciculata, with considerable increase in these zones of lipoid substances. In the medullar region no appreciable changes are observed.

Gland extracts in experimental carcinoma and sarcoma of albino rats. Gruhzit, O. M., Ann. Int. Med. **4**: 1589. 1931.

A series of albino rats were inoculated with either the Flexner-Jobling carcinoma or the Jensen sarcoma of rats. The treatment with extracts of suprarenal cortex or thymus failed to either inhibit or cause to regress the implanted carcinomas. The suprarenal cortex, thymus, omentum-lipoid and oxen testis extracts had no beneficial effect on the Jensen sarcoma of rats.—E. L.

The effects of adrenalin, ephedrine, and insulin on blood fat. Himwich, H. E. and M. A. Spiers, Am. J. Physiol. **97**: 648. 1931.

Dogs were injected subcutaneously with insulin or adrenalin or both, and fat, total solids of plasma, blood sugar, and lactic acid were estimated. It was found that insulin lowered the post-absorptive level of the plasma fat, while adrenalin in moderate doses invariably raised the level. As might be expected, when both of these endocrine products were injected into the same animal an antagonism was exhibited, adrenalin or insulin being predominant according to the magnitude of their respective dosages. Adrenalin in small amounts, however, caused a decreased concentration of blood fat. Ephedrine injections always produced a rise in the level of blood sugar, but the effects on plasma fat and blood lactic acid were not so consistent. Insulin successfully antagonized the effects of ephedrine on fat and sugar. Under the present experimental conditions it was not possible to demonstrate a diminution in the concentration of blood lactic acid as an action of insulin.

—Authors' Summary.

The secretion of the small intestine. II. The effect of insulin and adrenaline upon the secretion of the small intestine and its mechanism. Matsubara, M., Proc. Imp. Acad. **7**: 208. 1931. Abst., Chem. Absts. **25**: 4938.

The response of the secretion of the small intestine to subcutaneous injections of insulin is not always the same. In a majority of cases the secretion decreases. The enzyme content is usually determined by the amount of secretion, but occasionally the enzyme concentration per cc. excreted is lowered. The decrease of secretion stops as soon as an intravenous injection of d-glucose is made, yet when the hypoglucemia is re-established, the decrease of secretion again becomes manifest. After a subcutaneous injection of adrenalin there is a reduction of intestinal secretion, appearing in 1-3 hours. After adrenalin the enzyme secretion drops with the total volume of secretion, but the enzyme concentration per cc. may be relatively increased. Injections of adrenalin are

followed by an undoubted hyperglucemia. After section of the vagi, the effect of insulin on intestinal secretion is absent, while that of adrenalin is still found.

Effect of insulin on the blood cholesterin in non-diabetics (Influence de l'insuline sur la cholestérinémie chez les sujets non diabétiques).

Effect of folliculin on the blood cholesterin (Influence de la folliculine sur la cholestérinémie).

Effect of adrenin and ergotamine on blood cholesterin (Influence de l'adrénaline et de l'ergotamine sur la cholestérinémie). Neumark, S., Compt. rend. Soc. de biol. **104**: 1123, 1125, 1126. 1930.

Ten to 20 units of insulin administered subcutaneously gave irregular results. Folliculin gave a slight rise followed by a reduction. Adrenin gave irregular results.—J. C. D.

Possible constitutional elements in the behavior problems of the young. Rowe, A. W., Endokrinologie, **9**: 179. 1931.

The author has selected a group of 104 children, all of whom present behavior problems, from a larger consecutive series of 650, all of whom have had very thorough diagnostic studies. Analysis of the physical status of these children shows a striking incidence of cases with pituitary dysfunction or hypofunction and a second group with primary lesions of the central nervous system, of traumatic or disease origin. Tables are given collecting many of the objective features of the studies. The author finds that, independent of primary etiological classification, there is a common evidence of gross metabolic error throughout the entire series. He concludes, "The inference which the writer feels may be warrantable from this analysis is that the agencies which effect metabolic levels, be it directly or indirectly, through the hormone control of the endocrine glands or through the manifold intrinsic functions of the nervous system, through one or both, working independently or together, that such agencies may be associated with the mental status engendering a behavior problem." The paper is regarded as a preliminary communication pointing the way to extensive further studies.—Author's Abst.

Injections of testicular extracts in capons. Quantitative effect of the male hormone on the growth of the comb (Injection d'extrait testiculaire a des chapons. Action quantitative de l'hormone male sur la croissance de la crête). Benoit, J., Compt. rend. Soc. de biol. **104**: 1332. 1930.

Alcoholic extracts of testis treated with ether and acetone and preserved in olive oil were used. Capons, in which no signs of residual testicular material were evident after periods up to a year or more, were given graded doses of the extract. The increase in the size of the comb was, within limits, proportional to the dose.—J. C. D.

Effect of injections of urine from men and children on the genital tract (L'influence des injections d'urine d'homme et d'enfant sur le développement du tractus génital du rat impubère). Bourg, R., Compt. rend. Soc. de biol. **104**: 1048. 1930.

The dose used was 1 cc. of urine daily for about 4 weeks. Male urine produced an increase of interstitial tissue with hypertrophy of the testis and genital tract. This result was much less marked than with the urine from pregnant women. No change appeared in the genital tract or ovary of female rats. Urine from male children, aged 3 to 7, was without effect in either sex.
—J. C. D.

Action of aqueous extracts of human placenta on the genital tracts of young rats of both sexes (Action de l'extrait aqueux de placenta humain sur les tractus génitaux du rat impubère male et femelle). Bourg, R., Compt. rend. Soc. de biol. **105**: 466. 1930.

The placenta from a three-months pregnancy was washed free of blood. A water extract from it when injected into young rats gave the same stimulating effect on the genital tract as that produced by injection of the urine from pregnant women.—J. C. D.

Notes on a hormonal test for pregnancy (A propos du test hormonal de la grossesse). Brouha, de Adele, Compt. rend. Soc. de biol. **106**: 6. 1930.

Intravenous injection of suspected urine into virgin rabbits about 1 kgm. in weight produces after 15 hours, if it is from a case of pregnancy, the appearance of characteristic follicular haemorrhages. These are easily seen with the naked eye. The test is more easily read than with mice, is more rapid and just as reliable.—J. C. D.

Moulting and castration in Rouen ducks (Mue et castration du Canard de Rouen). Caridroit, F. and V. Régnier, Comp. rend. Soc. de biol. **105**: 435. 1930.

Castration in March when the birds have their winter plumage results in an early moulting. The subsequent plumage is of the winter, not the summer type. If the operation is performed in May at the start of the spring moulting, the usual sequence of events is not disturbed, the birds acquiring their summer, and after an October moulting, their winter plumage.—J. C. D.

The periodic sex cycle and folliculin (Cycle sexuel périodique et folliculine). del Castillo, E. B. and C. J. Calatroni, Compt. rend. Soc. de biol. **104**: 1024. 1930.

In normal female rats, daily doses of 0.10 to 0.25 units of folliculin continued over periods up to 6 months caused a decrease in the dioestrous. In spayed animals such doses gave rise to a fairly regular sexual cycle. In the normal animals, maturation of the follicles did not take place.—J. C. D.

Hormonal control of lactation; non-effect of corpus luteum; positive action of extracts of hypophysis. Corner, G. W., Am. J. Physiol. **95**: 43. 1930.

The administration to non-pregnant spayed rabbits of corpus luteum extract (progestin) did not cause proliferation of the mammary gland beyond the stage normally attained at puberty. The continuous presence of corpora lutea in the ovaries, during a period equal to that of normal gestation (brought about by experimental means) was equally ineffective in altering the mammary gland. Administration of extracts of whole sheeps' hypophysis to spayed virgin rabbits caused proliferation of the mammary gland and simultaneous lactation, producing in two weeks a condition scarcely distinguishable from that present at the full term of gestation. Previous preparation by action of the corpus luteum was found not to be necessary to this effect.

—Author's Summary.

Do large doses of folliculin when injected have an effect on the Graafian follicle (La folliculine, injectée a fortes doses, a-t-elle une action sur l'ovisac en maturation)? Courrier, R., Compt. rend. Soc. de biol. **104**: 282. 1930.

Folliculin injected into guinea pigs during the week preceding parturition suppresses the power of forming deciduomata ordinarily possessed by the uterus shortly post-partum. The corpora lutea of lactation are present and apparently normal. If the follicles are examined before rupture, an unusual amount of chromatolysis is found in the cells of the granulosa.—J. C. D.

Folliculin and the uterine changes preparatory to implantation of the egg (Folliculine et phénomènes utérins préparatoires a la nidation de l'oeuf). Courrier, R., Compt. rend. Soc. de biol. **104**: 1178. 1930.

Folliculin was administered to rabbits in large quantities during the early phases of the activity of the corpus luteum. This inhibits the changes which take place in the uterus preparatory to the implantation of the egg, and which are dependent on the corpus luteum.—J. C. D.

Metabolism of women during the reproductive cycle. IV. Calcium and phosphorus utilization in late lactation and during reproductive rest. Donelson, E., H. A. Hunscher and I. G. Macy, J. Biol. Chem. **91**: 675. 1932.

In spite of a calcium intake of 2 to 4 grams per day, calcium balance determinations for 3 women at the close of the 62nd, 63rd, and 65th weeks of intensive milk flow indicated a loss of calcium in contrast to a storage of this

element at corresponding periods in the preceding lactation in which there was a long, progressive decline in the output of milk. The cumulative effect of progressive demands imposed on the maternal organism by preceding pregnancies and subsequent periods of milk flow, following in very close succession, has been given as a possible explanation of the negative calcium balances. There was a storage of phosphorus in all cases at the close of 14 months' milk flow and in the lactation periods observed. During the postlactation periods, at the 3rd and 12th months after cessation of milk flow, calcium losses and phosphorus storage were indicated.—Icie G. Macy.

Hormone therapy with intramuscular injection of pregnancy blood in disturbances of menstruation (Hormontherapie durch intramuskuläre Injektionen von Schwangerenblut bei Menstruationsstörungen). Esch, P., Zentralbl. f. Gynäk. **54**: 19. 1930.

Ten cc. of blood taken from a pregnant woman and mixed with 1 cc. of 2% citrate solution was injected immediately into the gluteal muscles of a patient with menstrual disturbance. Injections were made first every third day, then every second day, and then every day. In some cases 20 cc. daily was given. Eighteen cases are reported. The results were negative in some, positive in others (particularly amenorrhoea with hypoplasia). The mechanism of the reaction is not explained; the indications for treatment are too vague; the number treated too few, and the results too contradictory to permit any positive conclusions to be drawn.—A. G. Klein.

Ovogenesis and the normal follicular cycle in adult mammalia. Evans, H. M. and Olive Swezy, Mem. Univ. Calif. **9**: 119. 1931.

Ovogenesis in the rat, guinea pig, dog, cat, and man occurs throughout the whole period of sexual life in a rhythm fundamentally related to the ovulation cycle. In all cases the new birth of eggs occurs in large numbers throughout metoestrum and anoestrum. In the latter phases of this production a striking picture is produced in the ovary. The final maturity and ovulation of a selected group of follicles or a single follicle involves the destruction of all remaining follicles. In the dog and cat this extensive production and sweeping destruction of follicles is an impressive phenomena. The destruction seems complete, and immediately following ovulation the next succeeding ovogenetic wave begins. This is called the "follicular cycle." In the rat, guinea pig, and dog, the follicular cycle coincides normally with oestrous cycle. In the cat the two cycles may or may not coincide. In man the follicular cycle has no necessary relation to the menstrual cycle, ovulation taking place at any time during the latter cycle. The ova arise by proliferations from the germinal epithelium in the form of invaginations or cords, forming groups of epithelial cells which are cut off from the epithelium and pass through the tunica albuginea. From one to many cells in each group enlarge and develop into sex cells, the remaining epithelial cells in the group forming the follicle cells. Extensive degeneration of the sex cells is a normal process in each cycle. This occurs to some extent at all periods but reaches its maximum at anoestrum or prooestrum, extending into the next cycle, and resulting in the almost complete destruction of the enormous numbers formed during that cycle. It occurs at all stages of growth of both ova and follicles. Degeneration usually begins in the granulosa cells but occasionally the first indications may be found in the ovum. In polyovular follicles one or more ova usually degenerate before the others. Oestrum marks the end of the preceding wave of ovogenesis and follicular development and the beginning of the next wave in the rat, guinea pig, and dog. It is the period at which the newest sex cells, other than atretic ones, are to be found in the ovary. In the cat and man the ovulation period marks the end of one wave and the beginning of the next. New sex cells are formed at all periods of the cycle but the number of these increases gradually, beginning with early metoestrum, to the end of the cycle. During late pregnancy and in anoestrum and prooestrum very large numbers are present. During pregnancy the rhythm of the follicular cycle is not obliterated. In the rat, which has a gestation period of four or five times the length of the oestrous cycle, four or five cycles of the production of eggs and follicles and their degeneration occur during the period. Recurring cycles are also found in the guinea pig. In the rat the number of ova produced is smaller than in the other mammals but the sequence of events in the follicular cycle is the same, though the short length of the cycle results in a telescoping of the dif-

ferent phases. In man, there is the same evident relation of ovogenesis to the ovulation cycle which seems to characterize the mammalia generally. Ovulation in man seems to occur at approximate intervals of twenty-eight days. This rhythm bears no exact or invariable relation to the menstrual cycle. The preliminary maturation phases so characteristic of the male germ cells, are found in the ova of these adult mammals. In the monkey, the follicular cycle has been only partially investigated. Ovogenesis takes place in the same manner as in the other mammals. Ovulation apparently takes place at any time in the menstrual cycle. The concept that, in the mamalia, the ova are all formed before birth and remain quiescent until sexual maturity calls them into activity, has no foundation in fact. On the contrary all the ova of adult life are new formations and are being constantly produced and as constantly destroyed. These processes are part of the rhythmic production and destruction of the tissue in the generative tract which is without parallel in any other organ in the body, the sex cells having probably the shortest life span of any cells in the body.—Authors' Abst.

Studies on uterine hemorrhage; relation of hemorrhage to events of menstrual cycle and to pathologic findings. Fluhmann, C. F. and Dorothy L. Morse, Am. J. Obst. & Gynec. **21**: 455. 1931.

An analysis of 1137 cases of abnormal uterine bleeding showed that 630 were associated with pregnancy, while 507 cases were in non-pregnant women. The latter patients were classified into 8 distinct categories, according to the clinical manifestation of the hemorrhage. (1) Menorrhagia, or profuse or prolonged flow in patients with otherwise normal menses. The sequence of events of the menstrual cycle in the ovaries and endometrium is undisturbed. The most frequent etiologic factor is any condition which interferes with the contractile power of the uterus or results in a hyperemia of the pelvic organs. (2) There is an irregularity in the time factor, the menstrual periods appearing too frequently, or are delayed, or are totally irregular in their occurrence. The main etiologic factor is to be sought in disturbances of ovarian function, which may be of a primary endocrine nature or secondary due to anatomic lesions. (3) (a) Hemorrhage initiated with a menstrual period may continue for a prolonged length of time. In these cases are mainly found lesions intimately connected with the endometrium, such as submucous fibromyomas and endometrial polyps, or definite pathologic changes such as hyperplasia of the endometrium or endometritis. (b) Continuous bleeding may set in during the stage of endometrial proliferation. The physiologic explanation may be found in a sudden destruction of the corpus luteum due to extension of an inflammatory process. (c) Bleeding during the endometrial stage of secretion is of unusual occurrence, and may be partly due to the premenstrual hyperemia of the pelvic organs. (4) Hemorrhage may occur in the middle of the menstrual cycle at a time corresponding to the rupture of the graafian follicle, the so-called "ovulation bleeding." (5) A type of hemorrhage characterizing hyperplasia of the endometrium is found when the menstrual periods become progressively more profuse or irregular and end finally in continuous bleeding. (6) Bleeding may occur following a period of amenorrhea in nonpregnant women of the childbearing age due to (a) hyperplasia of the endometrium, or (b) a traumatic or ulcerative lesion of the uterus following a previous removal or destruction of the ovaries. (7) Hemorrhage may occur at irregular times and without any connection with the events of the menstrual cycle, due to traumatic or ulcerative lesions of the cervi or endometrium resulting from new growths or inflammation. (8) Irregular hemorrhage due to the same causes as in Group 7 may occur in women past the climacteric. In rare cases ovarian newgrowths may also affect the endometrium and produce bleeding.

—Authors' Summary.

Experimental cryptorchidism in immature guinea pigs. Early effects (Cryptorchidie expérimentale chez le cobaye impubère ses résultats précoces). Foncin, Mme. R., Compt. rend. Soc. de biol. **105**: 982. 1930.

Guinea pigs three weeks old weighing 180 to 200 grams were used. The germinal epithelium started to degenerate within four days and never recovered. The interstitial tissue developed rapidly as usual when the animal weighed about 350 grams. At the same time the genital tract and accessory organs developed as in normal animals.—J. C. D.

Effect of repeated injections of urine from pregnant women on experimental cryptorchid testes in guinea pigs (Action des injections prolongées d'urine de femme gestante sur testicules de cobayes en cryptorchidie expérimentale). Foncin, Mme. R., Compt. rend. Soc. de biol. **107**: 1023. 1931.

Daily injections of 2 cc. of urine for two weeks produce a rapid growth of the seminal vesicles and interstitial tissue but none of the tubular tissue. Further injections up to 35 do not augment the development but produce a regression. If the animals are not examined till one or two weeks after the last injection the effects largely disappear and the genital tracts resemble those of the uninjected animals.—J. C. D.

Follicular hormone (L'ormone follicolare). Frattini, B. and M. M. Maino, Archivio dello Institute Biochimico Italiano, **2**: 3. 1930.

The authors have obtained in crystalline form the follicular hormone, hormone from the ovary and from the urine of pregnant women. It fails to give the biuret, the millon or the xanthoproteic reaction, containing no nitrogen. It assays one Allen rat unit in 0.2 mgm. It is proposed to establish as the most reliable unit the last amount of the substance that gives complete estrus in all test animals.—R. G. H.

Multiple ovaries and the oestrous cycle in the white rat. Friedman, J. L. and L. B. Nice, Am. J. Physiol. **95**: 40. 1930.

Multiple ovarian transplants in normal female rats nearly doubled the number of oestrous cycles as demonstrated by the vaginal smear method. The voluntary activity of these rats was not markedly increased after the operation. Pseudo-pregnancy was induced in 10 of the 19 animals by the glass rod stimulation of Long and Evans. Exposure to a vasectomized male produced this condition in nine of these rats.—Authors' Summary.

Further observations on ovarian transplantation. Hannan, J. H., Brit. M. J. **1**: 137. 1931.

Five human ovaries were transplanted into monkeys (Macacus rhesus). Some of these were placed between the layers of the broad ligament and the others subcutaneously. As in his previous experiments where ovaries were transplanted from rabbit to rabbit and cat to rabbit, the grafted ovaries failed to continue their physiological function. The author believes that the follicular mechanism continues only a few weeks after transplantation.—L. B. Nice

Influence of ovarian grafts on the seminal vesicles (Action de la greffe ovarienne sur les vésicules séminales). Houssay, B. A., L. Giusti, J. M. Lascano and Gonzales, Compt. rend. Soc. de biol. **107**: 1203. 1931.

In 6 uncastrated male guinea pigs ovarian grafts produced a marked enlargement of the seminal vesicles. In castrated animals the vesicles atrophied, whether ovarian grafts, folliculin injections or hypophyseal transplants were used. The ovarian grafts, it is suggested, stimulate the testis activating secretion of the hypophysis and the testis in turn stimulates the vesicles.—J. C. D.

Masculine sex hormone from urine and its assay by the comb method (Männliches Geschlechtshormon aus dem Harn und seine Prüfung an Vögeln). Kabak, J. M., Endokrinologie, **9**: 84. 1931.

By chloroform extraction and purification of acidified urine of men a potent extract was obtained. This caused marked growth in the combs of castrated chickens. Similar results were obtained with extract from the urine of women. Question is raised as to the specificity of the comb test.—R. G. H.

A note on the problem of the oestrus-cycle in parabiotics (Notiz zur Frage nach den Oestruszyklen bei der Parabiose). Kahn, R. H., Endokrinologie, **8**: 262. 1931.

With the increasing number of studies on animal parabiosis the results become more and more contradictory with respect to such problems as oestrus, pregnancy, and milk secretions. Even the author has found contradictory re-

sults in parabiotic animals. With such a state of affairs, it would seem that we should give greater weight than has been given heretofore to parabiosis as in rare instances it occurs in nature. Such a case, for example, is that of the Siamese twins, Josefa and Rosa Blazek, who were observed by the author during the pregnancy of one of the sisters. These two girls had menstruated regularly and simultaneously from the 13th year. During the pregnancy of the one, menstruation continued in the other up to the eighth week of term. In both individuals the mammary glands enlarged and in both milk was secreted. The fact seems clear from this Blazek case that when intimate connection between the two parabiotic cases exists for a sufficiently long time, the oestrual cycles come together; that pregnancy of the one may co-exist with menstruation of the other, but that the latter ceases with the advanced stages of pregnancy. The author contends that such cases in which one may be assured that the interchange between blood streams is good are far more conclusive than are the instances of artificial parabiosis in which good unions are not long maintained. If such a case is offered again for study by modern methods, other things being favorable, the explanations of these phenomena may be found.—C. P. Stone.

Hyperfeminization in rabbits (Über Hyperfeminierung beim Kaninchen). Kallas, H. and A. Lipschütz, Bull. d'histol. appliq. á la. physiol. **6**: 273. 1929.

Hyperfeminization of the castrated male rabbit can be effected by intrarenal ovarian transplantation. The effect on the teats is by no means so striking as in the guinea pig. But if the mammary gland is examined by the methods as indicated by Ancel and Bouin the effect becomes extremely striking. In two cases the macroscopical aspect of the mammary gland was similar to that in pregnancy. In one case there was even milk secretion. The ovarian graft behaved similarly to that in the castrated male guinea-pig: there was great follicular development, but corpora lutea were absent. Haemorrhagic follicles as in the normal rabbit's ovary were present.—A. Lipschütz.

Prognosis and therapy of arthropathia ovaripriva (Prognose und Therapie der Arthropathia ovaripriva). Lauber, H. J. and C. Ramm, München. med. Wchnschr. **77**: 89. 1930. Abst., Am. J. Obst. & Gynec. **22**: 660.

The authors describe a type of joint affection, which develops during the menopause and is directly attributable to lack of ovarian hormone. They comment on reports of joint lesions, attributed to hyperthyroidism and other endocrine disturbances. Arthropathia ovaripriva is characterized at first, by tingling and pain, particularly in the small phalangeal, and later in the carpometacarpal joints, and finally in the knee-joints. These symptoms are particularly noticed when the patient moves from cold outdoor temperatures into a warm room. They are probably due to vascular spasm. Objectively, the joints are found thickened and slightly swollen. Motion, active and passive, is limited and painful. There are no signs of acute inflammation. X-ray shows very little in early cases; in late cases, changes similar to those of arthritis deformans are seen. The important feature of the treatment is the administration of an active ovarian hormone. In 6 early cases, the authors obtained cures by giving such a preparation by mouth (Ovoglandol or Menformon-Laqueur), in addition to potassium iodid and alternate hot and cold baths. Improvement was evident in three to six weeks, and complete cure in six to twelve weeks. Three late cases were improved, but not cured, by these measures plus baking, massage, diathermy, etc.

The nature of the substance causing ovulation in the rabbit. Leonard, S. L., Am. J. Physiol. **98**: 406. 1931.

The results of injecting several anterior pituitary preparations intravenously into adult rabbits and into immature rats are presented in an attempt to determine which of the known hormones of this gland is inducing ovulation in the rabbit. Pregnant urine containing both follicular stimulating and luteinizing hormones but no growth hormone will induce ovulation. A growth hormone (phyone) containing no follicular stimulating or luteinizing hormone for rats will induce ovulation in the rabbit. This same growth hormone will show antagonism to follicular stimulating hormones when both are injected simultaneously into immature rats. It was found that certain samples of urine

from castrate women, which produced only follicles in the ovaries of immature rats, would also induce ovulation only in large doses. Smaller doses of pregnant urine would cause ovulation but quantitatively the amount of follicular stimulating or luteinizing hormone from urinary sources, when tested on young rats, is not correlated with its ability to induce ovulation in the rabbit. Likewise, qualitatively, the sex influencing hormones and the growth hormone bear no relation in their ability to induce ovulation. The urine of pregnant cows containing none of the demonstrable anterior pituitary hormones will not cause ovulation. A follicular stimulating and luteinizing hormone prepared from a pyridine extract of sheep pituitary also was found capable of inducing ovulation though the minimal effective dose in either case has not been determined. In view of all these facts the possibility of an ovulating principle is suggested and discussed.—Author's Abst.

Absorption of follicular hormone through the mucous membrance of the gastro-intestinal tract (L'assorbemento dell'ormone follicolare per via gastrica). Maino, M., Archivio dello Istituto Biochimico Italiano, **2**: 495. 1930.

Follicular hormone administered orally to spayed rats produces full oestrus. Three times the amount necessary for subcutaneous injection is required. The length of time required to produce oestrus is the same by both methods. Results are independent of purity of the product. Alcoholic solutions are three times as effective as aqueous solutions. The rat experiments are well controlled.—V. Schelling.

Influence of the seminal epithelium on the hypophysis (Results of parabiosis) [Influence de l'épithélium séminal sur l'hypophyse (Expérience de parabiose)]. Martins, T., Compt. rend. Soc. de biol. **105**: 789. 1930.

The testes of rats and mice were transplanted to the abdomen where a partial degeneration took place. These animals were then parabiotically united to normal females. There was a prolongation of the active phases of oestrous but the effect was not as marked as with a completely castrated male. The testis therefore forms a hormone which modifies the secretion of the anterior lobe.—J. C. D.

Ovulation in pregnant rabbits after the injection of urine from pregnant women (Ovulation chez la lapine gestante, après injection d'urine gravidique). Martins, T. and M. Fabiao, Compt. rend. Soc. de biol. **105**: 791. 1930.

A single dose of the urine, detoxified by extraction with ether, was given intravenously. One sample of urine came from a woman with a hydatidiform mole. Examination forty-eight hours after the injection showed maturing follicles in the ovaries with no evidence of injury to the placentae or embryos.
—J. C. D.

Effect of insulin on the ovary (Action de l'insuline sur l'ovaire). Migliavacca, A., Compt. rend. Soc. de biol. **104**: 1266. 1930.

Four white rats received daily 5 units for a month while three others received 10 units for 20 days. Histological examination of their ovaries showed a cessation of ovulation due to the presence of numerous corpora lutea.
—J. C. D.

The presence of a virilizing substance in the urine of a young woman suffering from virilism (Présence de substances virilisantes dans l'urine d'une jeune fille atteinte de virilisme). Parhon, C. I. and Marie Briese, Compt. rend. Soc. de biol. **107**: 384. 1931.

Urine and blood serum were injected into immature rats and castrated guinea pigs. There was a distinct enlargement of the seminal vesicles as a result. This indicates the presence of substances with a specific stimulating action on the male reproductive tract.—J. C. D.

Studies on the cause of parturition in women (Recherches sur la cause de l'accouchement chez la femme). Perez, M. L., Compt. rend. Soc. de biol. **104**: 1021. 1930.

Citrated blood from women in active labor was injected into women who were past term without any signs of the onset of labor. In all of the 50 cases tested, evidence of the onset of labor appeared at once and in half of these was carried on to birth. In a control series with blood from women in the later months of pregnancy, the results were negative. This is evidence of the hormonal nature of the factor governing the onset of labor—J. C. D.

Testicular tubular adenoma of the ovary; its etiologic relation to embryonic vestiges and spontaneous sex reversal of the female gonads. Report of a case. Popoff, N. W., Arch. Path. **9**: 31. 1930.

A case is described of tubular testicular adenoma of the ovary which occurred in a woman free from any signs of hermaphroditism. Biologic observations and experimental data on sex reversal and gonadic disturbances of the ovary are presented and commented on, and the conclusion is drawn that morphologic peculiarities of the ovary and biologic factors determining sex differentiation offer a logical explanation of spontaneous reactivation of the medullary cords, and even of the germinal epithelium, with the consequent organoid transformation in a male and neoplastic direction. In studies of clinical material and in histologic research in the ovary, attention should always be given to a full recording of the observations in both gonads and to a quantitative study of the occurrence of gonadic disturbances on the right side. The large, clear, fat-laden cells found in tubular testicular adenomas and originating from epithelial elements of medullary or sex cords should not be confused with true interstitial cells of connective tissue origin. Embryologic considerations, zoologic observations and experimental data give every preference to the term sex reversal or intersexuality rather than the meaningless term hermaphroditism which is generally used now.—Author's Summary.

A convenient method for extracting folliculin (Sur un procede commode d'extraction de la folliculine). Ribiere, M. and L. Chiapponi, Compt. rend. Soc. de biol. **105**: 667. 1930.

A simple procedure is outlined by which 300 or more units per liter can be extracted from the urine of pregnant women.—J. C. D.

Basal metabolism rates in late pregnancy and the puerperium. Schwarz, O. H. and C. Drabkin, Am. J. Obst. & Gynec. **22**: 571. 1931.

In an effort to evaluate the conclusions of Sandiford and Wheeler concerning the foetal contribution to the total basal metabolism of the pregnant woman the authors have carried out a series of measurements on a group of 17 women in this condition. The studies comprised a daily measurement for 2 weeks ante partum and an equal interval post partum. Body weight and deviation of the observed from the predicted basal rate is tabulated. The authors find a scatter in their observations which precludes the drawing of definite conclusions in regard to an increased energy production of the mother. The communication is designated as preliminary.—A. W. R.

Studies on the urinary excretion of oestrin, with especial reference to the effect of the luteinizing hormone and progestin. Smith, G. V. S. and O. W. Smith, Am. J. Physiol. **98**: 578. 1931.

Oestrin given in very large amounts to rabbits and humans was found only in traces in the urine, although physiological effects from the hormone were demonstrated. Eight pregnant women treated for threatened miscarriage by injections of luteinizing hormone showed a drop in the level of oestrin. This suggested that the corpus luteum might play a part in oestrin excretion. To three normal and three spayed doe rabbits 600-700 R.U. of theelin were given. Only between 22 and 67 R.U. were recovered in the urines. The administration of luteinizing hormone together with the same amount of theelin resulted in the recovery of from 300 to 500 R.U. of oestrin in the urines of the normal does, but in no increase of excretion in the spayed animals. Pro-

gestin given with theelin, however, caused an almost complete recovery of the 600 to 700 R.U. of theelin in both normal and spayed rabbits. It was therefore concluded that progestin causes the excretion of oestrin. It is suggested that this finding offers a means of testing for ovulation and corpus luteum formation in human amenorrhea cases, since in those cases whose urines were followed while they were receiving progynon, excretion was demonstrated only at the times when a corpus luteum was present. The possible physiological importance of the corpus luteum in promoting the excretion of oestrin during the menstrual cycle and early pregnancy is discussed.—G. V. S. Smith.

The application of oestrus hormone therapy in practice (Die Anwendung der Zyklushormontherapie in der Praxis). Streck, A., Ztschr. f. Geburtsh. u. Gynäk. **98:** 306. 1930.

The use of oestrus hormone preparations is indicated in the following cases: menstrual disturbances due to ovarian disorders, functional sterility, climacteric troubles, internal, nerve and skin diseases due to ovarian disturbances. It is not indicated in primary amenorrhea, genital hypoplasia, infantilism and polyglandular dysfunction. It is contraindicated in inflammations and neoplasms of the genital organs, in anemia and cachexia. The oestrus hormone preparation, "Progynon," is to be given by mouth and generally not to be used during menstruation. Dosage: 250 mouse units every second day. In cases of exceptionally severe hemorrhages, of juvenile metrorrhagia and dysmenorrhea 250 to 500 mouse units daily. If three periods of treatment of four weeks each have been unsuccessful Progynon is discontinued.—W. Raab.

Comparison of pregnancy tests. White, M. R. and A. O. Severance, J. A. M. A. **97:** 1275. 1931. Abst., A. M. A.

The authors found that in 191 Aschheim-Zondek reactions there were 20 instances in which the result did not check with the final diagnosis. There were five false positive reactions among 69 controls which were not pregnant. There were 29 observations in a group of ectopic pregnancies and incomplete abortions, 14 of which were negative. In only one case of pregnancy was the Aschheim-Zondek reaction negative. The Brouha reaction was uniformly positive in a group consisting of 60 normal pregnancies, 10 ectopic pregnancies and nine incomplete abortions. However, there were 10 false positive reactions in a series of 27 nongravid women. Four of these showed hypertrophy of the endometrium; three complained of menstrual irregularity, and one had tuberculous salpingitis. The Friedman test was observed in 40 cases. In the groups of normal pregnancies and nongravid controls there were 32 observations, all of which were correct with one exception. In this case, which proved to be a normal pregnancy, the reaction was carried out on the thirty-second day after the last menstrual period. There were four ectopic pregnancies, which gave two positive and two negative reactions. There were four incomplete abortions, three of which gave positive reactions. The tests of Aschheim and Zondek and of Brouha gave false positive reactions which probably depended on some endocrine disturbance. In such cases a consideration of the history usually prevents confusion. In the groups of ectopic pregnancies and incomplete abortions, the Aschheim-Zondek reaction was of value as a diagnostic procedure in 51% of the cases, whereas the Friedman reaction was of diagnostic value in 62% of the cases. The Brouha reaction was uniformly correct; however, this reaction does not lend itself as a practical diagnostic aid in cases of this type because of the time required for carrying out the test. In case of suspected normal pregnancy the Brouha reaction possesses distinct advantages over the Aschheim-Zondek reaction in that the results are determined macroscopically, and nearly mature test animals may be used. The advantages of the Friedman reaction are that only one test animal is required and that the reading may be made macroscopically at the end of from 24 to 48 hours. In view of the authors' own experience and that of others who have reported a total of 300 observations, they believe that the Friedman test is a dependable biologic reaction and a suitable laboratory procedure. The tests of Aschheim and Zondek, of Brouha and of Friedman depend on a quantitative change in the amount of active principle that is excreted in the urine during pregnancy. This active principle is presumably anterior lobe hormone. A substance specific to pregnancy has not been demonstrated. The serum test of Manoilov and the pupillary reaction of Bercovitz have been of little value as diagnostic aids.

Diffusibility of "female sex hormone" into the spinal fluid and its relationship to the oxytocic activity of the spinal fluid. Whitehead, R. W. and O. L. Huddleston, J. Pharmacol. & Exper. Therap. **42**: 197. 1931.

Commercial preparations of "female sex hormone" (Amniotin and Estrogen) were injected intravenously into unanesthetized dogs weighing from 5.1 to 21 kgm. A standard dose of 100 rat units was injected into each animal. Cerebrospinal fluid was withdrawn by cisternal puncture at varying intervals of 1 to 4 hours following the injection of the preparation. Each sample of cerebrospinal fluid was tested for both its oestrogenic and oxytocic activity. The oestrogenic activity was determined by injecting the unconcentrated spinal fluid subcutaneously in doses of ½ to 1 cc. into castrated rats and mice; the presence or absence of oestral changes induced thereby was determined by microscopic examination of the vaginal smears. The oxytocic activity was determined by adding 1 to 3 cc. of spinal fluid to the solution surrounding an isolated guinea pig uterus. The calcium and hydrogen-ion concentration of the spinal fluid and solution in which the guinea pig uterus was immersed was controlled by using the technique described by Van Dyke, Baily and Bucy. In 13 of the 16 experiments performed oestral changes were shown by the spayed rats and mice which were injected with spinal fluid. These results indicate that the "female sex hormone" had diffused from the blood stream into the cerebro-spinal fluid. Preliminary tests on Amniotin and Oestrogen performed by adding small quantities of these substances directly to the bath surrounding the uterine segment showed that each of these preparations contained an oxytocic principle. Likewise, the cerebro-spinal fluid was found to possess oxytocic properties after injecting these preparations intravenously into dogs. However, when a more highly purified preparation of Amniotin was obtained, it was found to contain no oxytocic principle. The cerebro-spinal fluid removed from dogs following the injection of this preparation likewise showed no oxytocic activity. Samples of the same spinal fluid yielded positive estrogenic results. It was therefore concluded from these experiments that: (1) The oestrus-inducing hormone diffuses rapidly from the blood stream into the cerebro-spinal fluid. (2) Certain "female sex hormone" preparations contain an oxytocic principle which is separate and distinct from the autocoid which is responsible for the induction of oestral changes in spayed rodents. (3) The oxytocic substance contained in certain "female sex hormone" preparations is likewise diffusible from the blood stream into the cerebro-spinal fluid. (4) No evidence was obtained to support the view that the "female sex hormone" stimulates the pars neuralis of the hypophysis, which, as has been stated, brings about an increase in the oxytocic activity of the cerebro-spinal fluid.
—O. L. Huddleston.

The catamenia and oxygen consumption. Wible, C. L., J. Lab. & Clin. Med. **27**: 14. 1931.

This study based on 22 individuals and involving 118 menstrual cycles showed, with one exception, a low oxygen consumption during menstruation. The results secured did not indicate a premenstrual rise in oxygen consumption. The period of greatest oxygen usage was indicated as being two weeks after cessation of menstruation.—Author's Abst.

Studies on the indications of the activity of the anterior lobe of the hypophysis according to age and species, by physiologic measurement of the hormone in the body fluids and the agreement of this with the evidence of morphologic activity in the thyroid (Recherches sur les indices d'activité de la préhypophyse selon l'age et l'espèce, par la méthods du titrage physiologique de l'hormone dans le milieu intérieur, et sur leur correspondance avec les manifestations morphologiques de l'activité de la thyroïde). Aron, M., Compt. rend. Soc. de biol. **106**: 609. 1931.

The histologic evidence of increased activity in young guinea pig thyroids was used to measure the amount of anterior lobe hormone. In guinea pigs and rats but not in rabbits the histologic condition of the animals own thyroid parallels the amount of anterior lobe hormone in the blood and urine as shown by its effect when injected into test guinea pigs.—J. C. D.

The specificity of the excito-secretory principle for the thyroid contained in extracts of the anterior lobe of the hypophysis (Sur la spécificité du principe excito-sécréteur de la thyroïde refermé dans les extraits de préhypophyse). Aron, M., Compt. rend. Soc. de biol. **105:** 974. 1930.

Guinea pig thyroids are stimulated by anterior lobe extract. Caseosane, essence of terebinthine, peptone and antitetanic serum do not produce an equivalent reaction as claimed by some authors.—J. C. D.

The mechanism of the hyperglycemia produced by extracts of the posterior lobe of the hypophysis (Sur le mécanisme de l'hyperglycémie post-hypophysaire). Benetato, G., Compt. rend. Soc. de biol. **106:** 502. 1931.

In rabbits injections of atropine did not effect the hyperglycemia. A comparison of the protein sugar with the free sugar indicates that a large part but not all of the increase comes from a freeing of the bound sugar.—J. C. D.

Pituitary therapy of alopecia. A preliminary report. Bengtson, B. N., J. A. M. A. **97:** 1355. 1931. Abst., A. M. A.

Five years ago a woman with Fröhlich's syndrome was treated with various pituitary preparations. During the treatment, she developed a luxuriant hair growth, in addition to regaining her normal sexual desires, re-establishing her menstrual cycle, and losing weight. The growth of hair was particularly remarkable in that the patient and her immediate female relatives (mother and two sisters) all had, since early youth, a scanty atrophic type of hair, prone to dryness and easy end-splitting. Inferring a relationship of the pituitary therapy to this patient's hair growth and its change in texture, the author began to study the effects of certain pituitary preparations in cases of alopecia. He reports on 16 patients, in all of whom the results were so striking that a preliminary report seemed desirable to render this treatment available for investigation by others, in spite of the relatively small number of cases. It seems that coincidence could be ruled out by the uniform success in these 16 patients, most of whom tried (one over a period of 23 years) various kinds of other treatments. The patients were taken in order of admittance and treated without preference or selection. The results secured might be anticipated on theoretical consideration. An endocrine motor mechanism for the growth of hair must a priori be postulated, and, in view of the intimate association of the sex glands to the development of hair and of the pituitary to the sex glands, this mechanism might reasonably be looked for among these glands. On the basis of his observations the author concludes that a definite therapeutic relationship seems established between certain alopecias and the pituitary gland preparations used. The anterior lobe was in most of the cases, the sole influence in producing the growths of hair obtained. The hypodermic use of pituitary gland secured more satisfactory and more rapid hair growth than oral administration, which on the whole is disappointing. The combination of hypodermic injections in large doses (2 cc.) and oral administration was found to give the most rapid response.

The posterior pituitary hormone in metabolism. I. The effect of pitressin upon the carbohydrate reserves of the normal rabbit. Bischoff, F. and M. Louisa Long, Am. J. Physiol. **97:** 215. 1931.

The effect of pitressin upon normal rabbits was studied, including establishment of the lethal dose and the pharmaceutical and physiological range, the comparison of effects of intravenous, subcutaneous, and continuous intravenous injections upon blood sugar and lactic acid, the determination of blood urea nitrogen, amino acid nitrogen, inorganic phosphorus, and cholesterol, constituents which might reflect changes in protein or fat metabolism, the determination of blood volume changes by following the oxygen capacity, and the comparison of the carbohydrate reserve in dosed and control animals. The production of hyperlacticacidemia was found to be as characteristic of pitressin as the production of hyperglycemia. Doses of pitressin which are effective in producing hyperglycemia and lactic acidemia in the rabbit are pharmaceutical and not physiological. They approach the lethal dose. Hyperglycemia and lactic acidemia do not run parallel. The toxic effect of pitressin is not reduced when given as a continuous intravenous injection and when so given may be

more pronounced than the effect of a single intravenous dose. Pharmaceutical doses of pitressin, whether given intravenously or subcutaneously, produce no changes in the glycogen reserves of the muscle outside the limits of normal expected variation. A possible but not clearly established increase in liver glycogen takes place. No changes outside the normal limit in the blood amino acid nitrogen, urea nitrogen, or cholesterol are produced. As measured by the oxygen capacity, a pharmaceutical dose of pitressin increases the blood volume by 10% in the course of three hours. The muscle sugar rises above the resting level during a pitressin hyperglycemia. The results have added to rather than diminished the obscurity which clouds any understanding of the physiological activity of the post pituitary hormone. Several questions capable of experimental investigation have been raised: (1) The effect of pitressin upon medullary adrenalectomized animals, and (2) the effect upon the rate of blood flow. (3) The observation that pitressin may produce a lactic acidemia without affecting the peripheral glycogen reserve suggests further investigation of fat metabolism.—F. Bischoff.

Hypophyseal hormone of anterior lobe (prolan) and the male gonad (Das Hypophysenvorderlappenhormon (Prolan) und die männliche Keimdrüse. Experimentelle Untersuchungen an Ratten). Boeters, H., Virchows Arch. f. path. Anat. **280**: 215. 1931.

One hundred eight-seven rats (82 controls and 105 test animals) from the same colony of carefully raised stock, were involved. Various amounts of prolan (from 1 to 1000 rat units) were injected, the entire dose being given in some cases within 2 to 3 days, and in others over a period of 25 days. It was found that prolan is effective in male rats only in the presence of the testis. It is not effective in castrated animals. Prolan stimulates the germinal epithelium in immature testes but no mature spermatozoa appear, hence full sexual maturity does not result. In prolan-treated immature female rats, pregnancy occurred in one case. In general, these females reach sexual maturity at the normal time. Too large a dose of prolan damages the germinal epithelium as shown by the sloughing of the germinal cells, giant cell formation and retrogressive changes in the supporting cells. These morphological and associated functional disturbances evidently delay sexual maturation. Large amounts of prolan regularly cause an increase in the interstitial tissue and may lead to an increase in the weight of the testis. However, this interstitial tissue increase is not very closely correlated with the amount of damage seen in the germinal epithelium. Prolan brings about no observable changes in the testis of full-grown rats. Senile gonads are not influenced by it. Apparently prolan activates the specific male hormone of the testis, but in which of the cellular elements the hormone is produced is still debatable. In some roundabout way prolan causes growth of accessory sex organs in the immature as well as in old animals. While a larger dose is necessary in the male rat than in the female, both male and female rats appear to be more sensitive to prolan than the mouse.—A. T. R.

The C/N ratio in hypophysectomized dogs on a diet lacking in vitamin B (La relación C/N urinaria en la avitaminosis B de los perros hipofisoprivos). Braier, B., Rev. Soc. argent. de biol. **7**: 323. 1931.

The C/N ratio and urinary creatin increase less in hypophysectomized dogs than in controls. Creatinin decreases more, the loss in weight is greater and no hyperglycemia occurs.—J. S. Lewis.

Squamous epithelial rests in the hypophysis cerebri. Carmichael, H. T., Arch. Neurol. & Psychiat. **26**: 966. 1931.

The normal hypophysis removed at necropsy in a group of 55 cases was studied by means of serial sections. Masses of cells resembling squamous epithelium in histologic appearance were found in 18 cases (32.7%). In the nine subjects who were less than 20 years of age, groups of cells resembling squamous epithelium were not found. The incidence of these masses of cells, which apparently were squamous epithelial in type, among the 46 adult subjects was 39.1%. It seems reasonable to attribute the origin of these groups of cells, which apparently were squamous epithelial in type, to rests of the former hypophyseal duct, and to accept their relation to the so-called tumors of the

hypophyseal duct; that is, if it is accepted that the rests cannot be identified in subjects who have not reached the age of 20 years, because at that time the cells of the rests are not sufficiently differentiated from the other epithelial cells in the neighborhood.—Author's Summary.

Action of the hypertensive and ocytocic principles of the posterior lobe of the hypophysis on basal metabolism (Action des principes rétropituitaires hypertensif en ocytocique sur le métabolisme basal). Castrex, M. R. and M. Schteingart, Compt. rend. Soc. de biol. **105**: 116. 1930.

Vasopressin did not affect the basal metabolism regularly but ocytocin raised the rate somewhat in 12 out of 13 patients injected.—J. C. D.

Histological changes in the hypophysis of guinea pigs during pseudopregnancy (Les modifications histologiques de l'hypophyse au cours de la pseudogestation chez le cobaye). Desclin, L. and L. Brouha, Compt. rend. Soc. de biol. **107**: 895. 1931.

Pseudopregnancy was induced in 18 guinea pigs by two means. In one group, the production of deciduomata eliminated any hormonal effects due to the fetus. In the other hysterectomy eliminated both fetal and uterine hormones. Hypophyses from both groups showed the cell changes typical of pregnancy and were indistinguishable from glands of normal pregnant animals.
—J. C. D.

Action of phloridzin on hypophysectomized toads (Action de la phlorizine sur les crapauds privés d'hypophyse). Di Benedetto, E., Compt. rend. Soc. de biol. **107**: 1193. 1931.

Five lots of five to ten toads each were studied. Unless the glandular lobe was present phloridzin did not produce a glycosuria, although it did bring about a marked hypoglycemia.—J. C. D.

Mode of action of hypophysis after castration, demonstrated by implantation experiments. Emanuel, S., Ugesk. f. laeger. **93**: 535. 1931. Abst., J. A. M. A. **97**: 750.

Emanuel describes experiments in which a considerably greater effect was obtained with hypophyses from castrated rats than with normal hypophyses. The experiments indicate that castration leads to an increase in the quantity of both the follicular and the luteinizing hormones, but with a change in their relative quantity, the content of luteinizing hormone becoming relatively greater, presumably because this hormone is retained while the follicular hormone is quickly eliminated. Various conditions indicate that the basophilic cells with vacuoles are important in the formation of hormones and it is assumed that at all events the luteinizing hormone is produced there.

Hormone of the anterior hypophysis. Evans, H. M. and Miriam E. Simpson, Am. J. Physiol. **98**: 511. 1931.

For assay of the anterior hypophyseal growth six "plateaued" female rats from five to eleven months of age are employed. In each individual case, growth cessation is proven by at least three weighings at five-day intervals. The "plateau" is defined as a maximal gain of ten grams in twenty days. Male rats are more variable than females in their capacity to respond to the growth hormone. Under the influence of the growth hormone, male rats are incapable of adding to their body substance to the degree which characterizes females. This is still the case after gonadectomy of both sexes so that male and female tissues react differently to the growth hormone. The growth as contrasted with that of their controls is exhibited best by injected gonadectomized females and least by injected normal males. Normal males are, however, always the greatest giants produced by chronic administration of the growth hormone. Animals suffer an actual loss of weight for from ten to fifteen days after administration of the growth hormone is stopped; their body weight is, however, permanently greater than that exhibited by their uninjected controls. Cessation of treatment entails no recession in the increased skeletal dimensions pro-

duced by the growth hormone. Sporadic congenital dwarfism is readily amenable to alteration by administration of the growth hormone. Implantation of anterior hypophyseal substance into senile male rats causes a definite increase in sex activity and increase in weight of the accessory organs of reproduction. Implantation of anterior hypophyseal substance into male rats rendered dwarfed and subnormal in their sexual physiology by inadequate vitamin G—increases markedly their sex activity, establishing normal behavior in fact within a fortnight. Implants or extracts of anterior hypophyseal substance cause marked hypertrophy of the mammary gland in the rat when the ovary is present but they are incapable of doing so after ovariotomy.

—Authors' Summary.

Urinary elimination of phosphates and phenol in fasting hypophysectomized dogs (Influencia del ayuno sobre la eliminación de fosfatos y fenoles urinarios en los perros hipofisoprivos). Gerschmann, R., Rev. Soc. argent. de biol. **7**: 350. 1931.

Excretion of phosphates in dogs fed with meat showed the same figures for hypophysectomized and normal controls. In complete fasting, operated dogs eliminate less than controls, the difference is more marked in dogs fed on protein-free diet. Operated dogs eliminate two-thirds of the amount of phenol eliminated by normal dogs when fed on meat. Complete fasting and protein-free diet accentuate the difference. The decrease in phosphate and phenol excretion in fasting runs parallel to the decrease in N excretion.

—J. S. Lewis.

Pregnancy reaction in juvenile male mice from injection of urine containing the sex hormone from the anterior lobe of the hypophysis (Schwangerschaftsreaktion bei der juvenilen männlichen Maus durch Nachweis des Hypophysenvorderlappengeschlechtshormons im Harn). Gostimirovic, D., München. med. Wchnschr. **78**: 5431. 1931.

Gostimirovic finds that not only urine from pregnant women, but also urine from women affected with amenorrhea, genital carcinoma, castration and menopause give a positive reaction in male mice, as indicated by enlargement of the seminal vesicles. Concentrated prolan A (according to Zondek's method) does not cause an increase in the seminal vesicles of the test mice. Thus male mice can be used to test for pregnancy, but because of the long time (5 days) required to get results, it is not very practical.—A. T. R.

Action of anterior pituitary extract on small laboratory and domestic animals (Hypophysenvorderlappenextraktwirkungen auf kleine Laboratoriumstiere und auf Haustiere). Grüter, F., Arch. f. Frauenk. **16**: 287. 1930.

Rabbits were the experimental animals principally used but mice, rats, cats, dogs, swine and cattle were also used. Anterior lobe extracts heated to 80° C. or higher lose their effect on the ovary. Cows were brought into heat by anterior lobe extracts; milk secretion likewise was stimulated in cows, goats and swine. Chemical study of the milk showed a definite increase in the mineral content. Removal of the thyroid gland at the time of treatment causes a marked fall of mineral content.—W. J. A.

Increase in number of blood cells associated with certain syndromes of hypophyseal and hypophyseal-tuber regions (La polyglobulie de certains syndromes hypophysaires et hypophyso-tubériens). Guillain G., P. Lechelle and Garcin, Compt. rend. Soc. de biol. **106**: 515. 1931.

In five cases showing clinical evidence of injury in the hypophyseal region the number of red cells and usually the number of white cells was definitely increased.—J. C. D.

The influence of hypophyseal preparations and various proteins on the specific dynamic action of proteins (Der Einfluss von Hypophysenpräparaten und verschiedenen Eiweisskörpern auf die spezifisch-dynamische Eiweisswirkung). Herzfeld, E., Deutsche med. Wchnschr. **56**: 1558. 1930.

The author mentions his previous work in collaboration with Frieder in which they showed that in cases of dystrophia adiposo-genitalis they were able to bring about a rise in specific dynamic action by the use of preparations of

various portions of the hypophysis (Praphyson, Pituglandol, Hypolantin, etc.). He then presents data showing that Prolan as prepared by the Aschheim-Zondek method from the urine of pregnancy has a similar and even greater effect than the previous preparations, and also, as shown by occasional determinations in some patients, brings about a concomitant lowering of the basal metabolism. These effects were obtained in males as well as in females. No effects, however, were observed with Tonephin or Orasthin, the pressor and oxytocic principles, respectively, of the posterior lobe. Ovarian preparations, and in particular folliculin, were similarly without effect both as regards basal metabolism and specific dynamic action. To determine what effect the nature of the ingested protein had upon specific dynamic action, test meals containing beef, liver, or cheese as the only protein constituent were fed to normal humans, and it was found that all of these had a definite and apparently similar effect in their specific dynamic action. The liver was not quite as effective as the other two protein sources, but the author believes this to be due to the longer time necessary to digest liver, as shown by Hoesslin, in comparison with beef or cheese. The author concludes that although the anterior pituitary is not the only factor concerned in specific dynamic action, it is nevertheless a factor of great importance.—A. M. Targow.

The demonstration of the antidiuretic component of the hypophyseal posterior lobe hormone and a substance producing increased blood pressure in the blood of nephropathic and eclamptic individuals (Über den Nachweis der antidiuretischen Komponente des Hypophysenhinterhormons und einer blutdrucksteigernden Substanz im Blute von Nephropathien und Eklampsien). Hoffmann, F. and K. J. Anselmino, Arch. f. Gynäk. **144**: 503. 1931.

Hoffmann and Anselmino state that for the first time they are able to isolate from the blood of nephropathic and eclamptic women posterior lobe hormone which they feel is the responsible factor for the production of these conditions. They were able, with the help of the method which they worked out, to isolate the antidiuretic component of the posterior lobe in the blood serum. The posterior hormone is united with the serum and is disturbed by weak alkaline reactions. Therefore, they used a weak acid reaction in other to isolate it from the blood serum. Further, isolation was done by ultrafiltration and the hormone passes over into the proteid free ultrafiltrate. They experimented with these antidiuretic substances taken from the blood of the nephropathic and eclamptic individuals. This substance gave the identical antidiuretic effect of the posterior lobe extract. The ultrafiltrate has the same characteristic alkali sensitivity of the posterior lobe extract. Both these substances are absorbed by talcum and destroyed by ultraviolet radiation. They prove that the characteristic effect is destroyed after treatment with alkali. In all cases having a high blood pressure, they are able to isolate this substance from the blood. They showed that this substance raised the blood pressure in rabbits by the method of Koch and Mies. Like posterior lobe extract, this filtrate does not have a severe antidiuretic effect after the second injection. There is one difference, however, between the ultrafiltrate which they isolate and the commercial posterior lobe extract. The commercial preparation raises the blood pressure only after intravenous injection, whereas in the substance they isolate there is also noticed increased blood pressure after subcutaneous injection. They summarize as follows: We have found that the blood of nephropathics and eclamptics with edemas contain an antidiuretic substance and that this antidiuretic substance is identical with posterior lobe secretion. In the blood of nephropathics and eclamptics with hypertension, we find a blood pressure raising substance that is probably identical with the blood pressure raising compound of the posterior lobe. Ultrafiltrates of non-pregnant and healthy pregnant women, in many examinations, did not give this principle.—R. C. Moehlig.

Phlorizine diabetes in dogs deprived of their hypophysis (Le diabète phlorizinique des Chiens privés d'hypophyse). Houssay, B. A. and A. Biasotti, Compt. rend. Soc. de biol. **105**: 126. 1930.

Seven dogs received 1 gram of phlorizine each intravenously and then 3 to 7 daily doses of 1/10 gram subcutaneously. There was a very high mortality due apparently to hypoglycemia. Glycosurea and nitrogen elimination were not as high as in phlorizinized controls.—J. C. D.

Action of the sex hormone of the hypophysis on male animals (Die Wirkung der Sexualhormone, der Hypophyse auf männliche Tiere). de Jongh, S. E., Pflüger's Arch. f. d. ges. Physiol. **226**: 547. 1931.

In a series of investigations involving about 50 young male rats and mice (including controls), treated with urine from women in early stages of pregnancy and which had been more or less freed from menformon by benzol extraction, it was found that the testis increased in size only slightly, if at all, with only slight changes in spermatogenesis. Apparently the testis early gives off large amounts of sex hormone which causes some of the genital organs (especially the seminal vesicles) to enlarge. The interstitial cells of Leydig underwent both hypertrophy and hyperplasia. These results are probably due to the B-factor of the hypophyseal hormone.—A. T. R.

Antagonism of menformon and hormones of anterior lobe of the pituitary (Antagonismus von Menoformon und Hormonen des Hypophysenvorderlappens). de Jongh, S. E. and E. Laqueur, Arch. f. d. ges. Physiol. **227**: 57. 1931.

In immature and mature male mice the effects of menformon and "anterior pituitary hormone" on the accessory genitalia were studied. The authors interpret their results as showing that relatively large doses of menformon (as high as 40 units) inhibit the usual stimulating effects of the "anterior pituitary hormone" on the accessory genitalia of the male. It was noted, however, that in males injected with "anterior pituitary hormone," menformon was incapable of producing testicular atrophy.—H. Friedman.

Silver impregnation of the capillary endothelium of the anterior lobe of the hypophysis (Eine Silberimprägnation der Kapillarendothelien im Hypophysenvorderlappen). Karplus, H., Anat. Anz. **70**: 325. 1930.

By means of a new cobalt or cerium and silver nitrate method for demonstrating the reticular apparatus, the endothelium of the capillaries of the anterior lobe of the hypophysis of cats and dogs were shown to have many fine radiations extending out from the nucleus in the form of ribs with anastomosing twigs.—A. T. R.

Acromegaly and diabetes (Acromegalie and diabete). Labbe, M., A. Escalier and G. Dreyfus, Ann. de méd. **29**: 222. 1931.

The authors feel that there is a relationship between acromegaly and diabetes. There are three theories regarding the action of pituitary: (1) Stimulation of the pituitary by pathologic processes. (2) Neutralization of insulin by the pituitary hormone. (3) A direct action on the islands of Langerhans. There are two types of diabetics, one a paradiabetic in which the diabetes is due to an adenoma of the hypophysis and a second a true diabetes of acromegaly which can be best treated by a rigid diet and insulin.—E. L.

On the relation between the hormones of the anterior lobe of the pituitary and clinical syndromes. Lambie, C. G. and B. P. Wiesner, Edinburgh M. J. **38**: 605. 1931.

Assuming that the anterior lobe secretes three hormones, a thyrotropic, a gonadotropic, and a growth promoting one, there are 27 possible combinations of normal, over- and under-secretion. Of these theoretical syndromes, 14 are well recognized clinically, seven other types have cases which may represent them. Six are not seen clinically. The symptoms of each type are discussed.
—J. C. D.

Pharmacological method for the valuation of the action of the anterior lobe of the hypophysis (Pharmakologische Methode zur Wertbestimmung der Hypophysenvorderlappenwirkung). Loeser, A., Arch. f. exper. Path. u. Pharmakol. **159**: 657. 1931.

A method for the quantitative evaluation of anterior lobe activity in 25-40 gram immature female rats is described. An acetone dried powder obtained from anterior lobe tissue was used as the standard preparation. The relationship between the dose and the percentage of animals in which estrus occurred at least once was determined and on this basis the rat unit is defined as that

quantity of material which within 100 hours will produce estrus in 50% of the experimental animals. This dose amounted to 35 mgm. of the powder, equivalent to 210 mgm. of anterior lobe substance. A single injection was given intermuscularly.—P. A. Katzman.

Functional differences in the hypophysis associated with sex (Différenciation fonctionnelle de l'hypophyse en rapport avec le sex). Martins, T., Compt. rend. Soc. de biol. **105**: 99. 1930.

Female white rats were parabiotically joined to gonadectomized males or females. If the partner was a female an irregular oestrus cycle occurred in both animals. The ovaries were enlarged and contained many corpora lutea. When a castrated male was used there was a permanent oestrous. The ovaries were enlarged and cystic. No corpora lutea were present. These changes in the ovaries are presumably controlled by the excess of hypophyseal secretion supplied by the castrated animal. The different response to a male or female indicates a sex difference in this secretion.—J. C. D.

The distributions and concentrations of water and halides in the blood and urine during diuresis-inhibition by pituitary extract. McIntyre, A. R. and H. B. Van Dyke, J. Pharmacol. & Exper. Therap. **42**: 155. 1931.

Posterior lobe pituitary extract, during diuresis-inhibition in the dog, usually caused a slight but definite increase in the water-content of erythrocytes and serum together with a slight fall in the halide-concentrations. The extract had no effect on the distribution of Cl. and Br. between erythrocytes and serum. This was found to be the case (a) when Br. was anomalously distributed and (b) whether the kidneys were intact or had been removed. The extract caused no definite change in the serum-halide concentration of nephrectomized dogs. The ratios of bromide to chloride-concentration in the samples of urine fluctuated widely in all experiments and bore no consistent relationship to the ratios found in serum. Our experiments indicate that in the dog, posterior lobe pituitary extract causes diuresis inhibition by affecting only the kidneys.—Authors' Summary.

Anterior hypophyseal hormone (prolan) and the male gonad (Hypophysenvorderlappenhormon (Prolan) und die männliche Gonade). Neumann, H. O., Zentralbl. f. Gynäk. **55**: 407. 1931.

As a result of injecting large doses (200-400 rat units) of prolan (Aschheim-Zondek) into immature male mice, the testes of the 40 test animals showed more activity in the germinal epithelium than was found in the same number of control animals as evidenced by an increased number of mitoses in spermatogonia and spermatocytes and by hypertrophy of the spermatocytes. The accessory sex organs (seminal vesicles, prostate, etc.) were much larger in the test animals —A. T. R.

Effect of different substances from the posterior lobe of the hypophysis on the coagulation of the blood (Action de diverses substances post-hypophysaires sur la coagulation du sang). Nitzescu, I. I., Compt. rend. Soc. de biol. **105**: 70. 1930.

In dogs and in rabbits there was a marked reduction in clotting time and increase in density of clot following injections of either, vasopressin or ocytocin. The effect was evident half an hour after the injection but lasted less than 2 hours.—J. C. D.

The use of an anterior pituitary luteinizing substance in the treatment of functional uterine bleeding. Novak, E. and G. B. Hurd, Am. J. Obst. & Gynec. **22**: 501. 1931.

The present report deals with the treatment of 51 cases of functional uterine hemorrhage by an anterior pituitary luteinizing principle derived from the urine of pregnant women. In 44 of these the treatment was successful in checking the bleeding, even though some of our patients were treated with preparations of somewhat uncertain luteinizing potency. Most of the failures were in this group. Previous efforts at the organotherapy of this condition

have been unsuccessful. Radiotherapy is very undesirable in young women, so that, because of the frequent intractability of functional hemorrhage, many patients have had to submit to repeated curettage. The characteristic ovarian finding in these cases is an absence of corpora lutea. The administration of progestin, if this were available, would be a rational plan of treatment. Progestin is not yet available for human administration, and its effects would, moreover, be purely substitutional, as it has no effect on the ovaries. The administration of the luteinizing hormone of the anterior pituitary (prolan B) can be expected to be more fundamental in its effects. This substance has been shown by laboratory studies to produce striking luteinization in the ovary, and the secretion of the lutein cells is progestin, the element lacking in functional hemorrhage. The hormone can be obtained from the urine of pregnant women, although its extraction is as yet somewhat difficult, and the preparations with which we have worked have been of very variable potency. With strongly luteinizing preparations, it has been possible to check functional hemorrhage in 27 of 29 cases. In 14 of our 51 cases the bleeding has ceased after a single injection, and in 12 after two injections. A large proportion of these cases were of the intractable and recurrent type, many having had from one to four or more curettements. With less potent luteinizing preparations, the results have been less impressive, but on the whole satisfactory. Our experience with the entire group has convinced us of the value of the treatment in functional hemorrhages, and of its even greater future possibilities. This opinion seems a compelling one even though, in the nature of things, the results cannot be controlled with the precision of laboratory experiments. The rapidity of the effect in many cases makes it seem certain that the immediate effect, at least, is not brought about through the production of lutein tissue and progestin by the ovary. We believe that this immediate effect is exerted upon the still unknown bleeding factor which is the immediate cause of the bleeding in functional hemorrhage, and which is influenced by far smaller dosage than would be required to produce histologic changes in the ovary. This view we base upon recent investigations on this bleeding factor and on studies upon the relative dosage required to bring about the various stages of estrus. These are discussed in the paper. It is hoped that improvements in results will come with improvements in the methods of preparation of this substance, and, quite possibly, in its preparation in water-soluble solid form. Whether the intravenous method of administering prolan will yield results more favorable than the intramuscular route remains to be seen.—Authors' Summary.

The diuretic hormone of the brain (Die diuretischen Hormone des Gehirns). Olivet, J., Münch. med. Wchnschr. **77**: 58. 1930.

Dry-fed rabbits were rendered polyuric by Eckhardt's puncture of the uvula of the cerebellum or the lateral part of the fourth ventricle (in one experiment by diencephalic puncture). With polyuria established, and usually twenty-four hours after puncture, the rabbit was bled and its deproteinated and concentrated serum injected into another animal whose urinary output was measured by means of a bladder fistula. In ten out of eleven experiments the sera from the punctured rabbits produced diuresis in the injected animals whereas similarly prepared sera from several normal control rabbits had no such effect. In four of the ten positive experiments there was a two- to three-fold increase in urine output, in the remaining six a greater diuresis up to a twenty-fold increase. Glycosuria accompanied the majority of these polyurias and the author puts forth evidence to show that these are independent phenomena. In a footnote he announces the subsequent discovery of a diuretic substance in the urine of these polyuric animals. The conclusion drawn is that diuretic substances are mobilized in the blood by stimulation of certain parts of the brain.—P. Bard.

Structure and development of pars tuberalis of the human hypophysis and its relation to the other portions of the hypophysis (Aufbau und Entwicklung der Pars tuberalis des menschlichen Hirnanhags in ihren Beziehungen zu den übrigen Hypophysenteilen). Pietsch, K., Ztschr. f. mikr.-anat. Forsch. **22**: 227. 1930.

The report is largely morphological. It is based on 25 human hypophyses, with attached tuber cinereum, chiasm and corpora mamillaria, of both sexes, varying in age from 7th month prematures to 76 years of age, and 7 human embryos 2-12 cm. crown-rump. Pars tuberalis arises from the anterior part

of the hypophyseal evagination. That portion which spreads out on the under surface of the brain (surrounding the infundibulum) is subject to wide individual variation. Pars tuberalis is rich in connective tissue and blood vessels. Typical acidophils and basophils may occur especially at the base where pars tuberalis is continuous with pars intermedia, using the latter in its widest sense. The typical cell of pars tuberalis is a small element with finely granular basophilic cytoplasm and a pycnotic nucleus. It arises from a cell with a vesicular nucleus and indistinct cell boundaries, which is identical with the chief cell of the anterior lobe. The nucleus seems to undergo a colloidal transformation, which is regarded as probably a secretory process. Similar cells are to be found in the anterior lobe, apparently as a result of basophilic cells losing their coarse granules. There are certain similarities between the cells of the human pars tuberalis and the cells of pars intermedia of the pig. On the contrary, there are no similarities between the cells of the so-called pars intermedia of the human hypophysis and the cells of pars tuberalis of man. That which is generally regarded as pars intermedia is divided by this author into four zones: (1) pars intermedia proper, which is usually a thin sheet of cells between the residual lumen and posterior lobe; (2) cystic region, composed of hollow outgrowths from the cranial portion of the hypophyseal cavity; (3) nuclear region, which arises from the middle tubercle of the hypophyseal cup and which becomes partly surrounded by two wing-like trabeculae of connective tissue, extending from the hilus; (4) transitional region, which lies between the preceding and pars tuberalis. These four areas together with pars tuberalis are therefore not regarded as a functional unit, but rather as special structural portions of the glandular hypophysis. The cells of the nuclear zone are essentially like the chief cells of the anterior lobe. It is argued that phylogenetically the function of pars intermedia has been assumed by the anterior lobe so that in man there is practically no intermediate lobe as a circumscribed morphological structure—it being embodied in the anterior lobe. Its cells change into anterior lobe cells. The basophilic cells which invade the posterior lobe and which arise from pars intermedia, are typical basophilic cells as seen in the anterior lobe proper.—A. T. R.

The hypophysis of an orang-utang, together with remarks on the so-called pars intermedia of man and man-like apes (Die Hypophysis eines Orang-Utang. Nebst Bemerkungen über die sogenannte Pars intermedia bei Menschenaffen und Mensch). Plaut, A., Anat. Anz. **68**: 408. 1930.

This is a description of the histology of the hypophysis of a huge 20-year-old male orang-utang which died in tuberculosis, with no pathological findings in the meninges or brain. The hypophysis appeared normal, measured 10x7 x4.5 mm. and weighed 0.33 gram. It is strikingly similar to the hypophysis of the chimpanzee (previously described by the author) and to the human hypophysis, particularly in the great reduction of the pars intermedia, which is represented by only a single layer of cells in some places. In other places the anterior lobe and posterior lobe are in contact, with no visible pars intermedia between. While he thinks it is permissible to speak morphologically of a rudimentary pars intermedia in the hypophysis of man, orang-utang and chimpanzee, it should be emphatically pointed out that it is far more important to consider whether it represents an independently functional structure.
—A. T. R.

The effect of anterior pituitary luteinizing hormone on the male genital organs (Über die Beeinflussung des männlichen Genitales durch den luteinisierenden Wirkstoff des Hypophysenvorderlappens). Reiss, M., H. Selye and J. Balint, Endokrinologie, **9**: 81. 1931.

By means of injection experiments in male rats it was shown that luteinizing hormone counteracts the stimulating effects of follicle ripening hormone as seen in the seminal vesicle walls. The Leydig cells as well as the seminiferous epithelium showed fairly marked lipoid content.—R. G. H.

Studies on the physiology of reproduction in birds. XXX. Control of the special secretion of the crop-gland in pigeons by an anterior pituitary hormone. Riddle, O. and P. F. Braucher, Am. J. Physiol. **97**: 617. 1931.

Two dorso-lateral areas of the crop (ingluvies) of doves and pigeons normally undergo an extreme enlargement at the end of the brooding period and

then secrete the "crop-milk" which is fed to the young. This complete glandular enlargement and functioning can invariably be induced in very immature and other non-brooding birds of both sexes by suitable extracts of the anterior pituitary and by such extracts only. This growth response in the crop-gland area occurs after previous section of its nerve supply and is therefore not regulated or conditioned by the nerves. All of the several effective extracts used were known to contain the sex maturity hormone in greater or less amounts; all may also have contained small amounts of the growth principle; all caused growth in the gonad and enlargement of thyroid and liver. The effective crop-gland stimulant is destroyed by heat. The "luteinizing" hormone, as obtained from pregnant urine, is entirely ineffective in eliciting this response in the crop-gland. This result, together with no effects or possibly with adverse effects on gonad growth (to be more fully considered elsewhere) makes it quite improbable that the luteinizing and maturity hormones are identical or even closely related substances. It is not now known whether the principle activating the crop-gland is the growth, the sex maturity, or a third and now unknown anterior pituitary hormone. Certain aspects of this problem are discussed. If this response of this special part of the crop mucosa of the pigeon is a specific response to the growth hormone, it provides the easiest and quickest known method of testing and standardizing that hormone. A clear macroscopic result is obtained in 72 hours, and active "milk" secretion occurs on the fourth or fifth day.—Authors' Summary.

Snuffpowder therapy of diabetes insipidus with various posterior pituitary preparations (Zur Schnupfpulver—Therapie des Diabetes Insipidus mit verschiedenen Hypophysenhinterlappenpraparaten). Rosenberg, M., Klin. Wchnschr. **9**: 152. 1930.

Rosenberg made some clinical observations on patients suffering from diabetes insipidus and concludes that the treatment of diabetes insipidus by using powdered extracts of the posterior lobe is beneficial and that he obtained good results in most of the cases. He used several German preparations in different form, "tonephrin," "pituiganum siccum" (Hennig) and "pitrophorin" (Schering). In some cases, he used the posterior lobe extract in the usual commercial form and made tampons of cotton soaked in this commercial extract. In other cases, he used powdered sugar or milk sugar but "tonephrin" is already prepared as a powder which may be used in the form of snuff. He cites several cases in which he had very good results from this treatment.—R. C. Moehlig.

Hypophysectomy and replacement therapy in the rat. Smith, P. E., Am. J. Anat. **45**: 205. 1930.

The anterior and posterior pituitary was exposed by a parapharyngeal (ventral) approach and removed with a cannula and negative pressure in rats. There was no rupture of the diaphragma sellae or apparent brain injury. The pituitary stalk and pars tuberalis of the hypophysis remained intact. A constant syndrome resulted from the operation. Following the operation, there was no further increase in general body weight for at least a five-month period. Usually the weight decreased at first and then remained nearly stationary. Skeletal growth was almost completely inhibited. The rats operated upon before maturity retained their infantile appearance; those operated upon when nearly full-grown developed a cachectic condition. The adrenal cortex, the thyroids, and the reproductive organs regressed in weight and underwent a pronounced atrophy. Follicular growth ceased and the ovaries became filled with interstitial tissue. The corpora lutea, however, persisted for an unusual length of time. In the male libido sexualis disappeared at once and spermatogenesis ceased. The liver, spleen, and kidneys also decreased in size. Thus the response of the viscera in the hypophysectomized rat is the opposite from that seen in acromegaly whether experimentally produced (Putman, Benedict, and Teel) or occurring clinically (Davidoff and Cushing). Daily anterior homeotransplants restored the hypophysectomized rats to a normal or nearly normal condition. The testes enlarged, spermatogenesis was resumed, and fertility and sexual activity were restored. In the ovaries follicles developed, but formed follicular and lutein cysts, as in the case of normal adult rats given pituitary transplantations. The other reproductive organs enlarged. With a cessation of treatment the restored reproductive organs again atrophied. The transplantations also caused an enlargement of the other viscera examined to

normal or nearly normal proportions. The atrophied thyroid epithelium and adrenal cortex became structurally normal. The posterior and anterior pituitary was nearly completely destroyed in a number of rats by injecting it with chromic acid, a temporal approach being used in this operation. The resulting syndrome, although showing considerable variability, was similar to that described above except as regards early and usually marked adiposity, while the animals hypophysectomized by the ventral approach either showed no unusual fat deposition or developed only a slight obesity after a period of five or more months. This makes it seem highly probable that the adiposity exhibited after the destruction of the pituitary by chromic acid is due to an injury of the hypothalamus.—M. O. L.

Simmond's disease: Fatal issue; necropsy findings. Case 6. Reported by Strauss, I. and J. H. Globus, Proc. New York Neurological Society, J. Nerv. & Ment. Dis. **72**: 566. 1930.

A woman of 53 complained of wasting and general weakness. One year previously she had begun to show evidence of lowered resistance, becoming subject to repeated colds, persistent cough and lost weight progressively. The loss of weight and the sapping of the strength advanced rapidly. Three weeks prior to her admission to the hospital, she had a gastrointestinal upset with diarrhea, moderate elevation of temperature and cramps, lasting about a week. There was marked emaciation with almost complete loss of all the subcutaneous fat tissue. She weighed only about 70 pounds (normal weight 110). There was no icterus. The blood pressure was 125/80. The hemoglobin was 58% with 3,000,000 red blood corpuscles. The Rehfuss test showed complete achlorhydria in spite of 0.5 mgm. of histamine. The gastric ferments were present. Roentgenologic examinations of the chest and the gastrointestinal tract were negative. The blood chemistry was normal. At autopsy aside from mild atherosclerosis of the vessels at the base of the brain and some dulling of the leptomeninges, the brain was normal. There was a peculiar yellowish-tan hue to the surface of the brain. The same ecru was seen on cut surface of the brain. The pituitary gland showed alterations typical of Simmond's disease: marked fibrosis of interstitial tissue and reduction in the glandular elements. The other glands were examined and they revealed no changes.
—R. G. H.

Anterior lobe of hypophysis and growth. Von Monakow, P., Arch. f. Neurol. u. Psychiat. **27**: 321. 1931.

Von Monakow makes the observation that, while the occurrence of acromegaly, gigantism and dwarfism, together with animal experimentation, points to a definite relationship between the anterior lobe of the hypophysis and the process of growth, very little opportunity has been afforded to prove this contention by the use of potent hypophyseal extracts in the human. For this reason, he cites a case of mongolism with infantalism in which he was able to stimulate growth with this type of substitution. A boy at six with unmistakable signs of mongolism and with a somatic development equal to three was given thyroid preparations. His development was stimulated for a time, but later practically ceased. At the age of fourteen, substitution of a preparation made from the hypophysis of growing animals was begun. Growth and development were definitely stimulated, as evidenced by the anthropometric and roentgenologic findings. Sex characters developed rapidly. When the substitution was withdrawn, the growth ceased until its resumption. The mental age, however, did not improve with the physical. The author points out that this result does not necessarily prove that the patient was suffering from an anterior hypophyseal deficiency since normal experimental animals may be made to grow quite as effectively as those which have been hypophysectomized.
—E. K. Shelton.

Attempted treatment of psoriasis with "Prolan" (pituitary anterior lobe hormone) (Ueber Versuche der Psoriasisbehandlung mit Prolan). Walinski, F., Deutsche med. Wchnschr. **56**: 833. 1930.

Since there has been noted by other authors an improvement of psoriasis during pregnancy the author of this article treated six patients during several weeks with Prolan and believes he has observed some improvement. The dosage was two to four injections weekly of 50 to 100 units each.—W. Raab.

The gonad-stimulating substances of the anterior lobe of the pituitary body and of pregnancy-urine. Wallen-Lawrence, A. and H. B. Van Dyke, J. Pharmacol. & Exper. Therap. **43**: 93. 1931.

The assay of gonad-stimulating principles (hebin) by the use of immature male and female rats is discussed. The method used is based on the weight of the seminal vesicles in the male, and the ovaries in the female. The preparation of a crude pituitary hebin from various sources is discussed. It is pointed out that while beef anterior lobes are a poor source for this substance, good yields can be obtained from sheep and pork pituitary bodies. Pituitary hebin, administered subcutaneously, can initiate oestrus in the hypophysectomized rat. Associated with oestrus, there occur follicular maturation and uterine changes. Crude pituitary hebin does not dialyze through collodion or parchment; it is heat stabile (90° C.). It may be extracted from pituitary bodies at both acid and alkaline pHs. Hebin from pregnancy-urine does not dialyze through collodion or parchment; it deteriorates when boiled in aqueous solution. Urinary hebin stimulates the testis and ovary with equal facility; pituitary hebin, on the other hand, stimulates the ovary in a much smaller dose than that having a moderate effect on the testis.

—Authors' Summary.

Contributions to the comparative physiology of the frontal lobe of the hypophysis. Zavadovsky, B., T. Vinogradova and Sarafanov, J. Medico-Biologique, **2**: 32. 1930.

The principle findings of Zondek have been completely confirmed in this work regarding the stimulating action of the frontal lobe of the hypophysis on the sexual ripening in infantile mice. The activity of hypophysis of different classes of animals have been studied by implanting a given amount of the hypophysis-substance under the skin of infantile mice. In contrast to Smith's and Engle's suggestion, the hypophysis of birds (chicken) has been found to be very active—even more than that of dogs. The activities of the frogs' hypophysis and of that of the dog are found to be very close. The activity of the axolotl's hypophysis is strikingly low in comparison to that of other animals. It has been shown that the oestrus reaction in infantile mice activated by the hypophysary hormone appears even when there are no corpora lutea in the ovary—not even any trace of follicle ripening. Thus oestrus under these conditions takes place evidently as a result of the action of the follicle-hormone which is being produced by the whole mass of follicle of the hypertrophied ovary.—Authors' Summary.

The anti-diuretic action of extracts of the posterior lobe of the hypophysis (Sur l'action anti-diurétique de l'extrait rétrohypophysaire). Zunz, E., Compt. rend. Soc. de biol. **104**: 795. 1930.

Six dogs with vesicle fistulas were studied after subcutaneous injections of vasopressin, pituitrin, and ocytocin. The first had some anti-diuretic action, the second a marked effect, but the most striking results were obtained with the ocytocic hormone.—J. C. D.

Maternal and fetal blood sugar changes under various experimental conditions. Britton, S. W., Am. J. Physiol. **95**: 178. 1930.

Comparison has been made in different animals (chiefly cats) of maternal and fetal blood sugar changes under various conditions. Under insulin the blood sugar in the mother falls readily to the convulsive level; concurrently in the fetus the glucose percentage is notably higher, however, and it may be within normal limits. Even when convulsions are allowed to extend for two hours, the sugar values are slightly in favor of the fetus. The conditions do not hold in very young fetuses, or when the mother is anesthetized before making (Caesarean) delivery. Normally in the later stage of pregnancy, which was the period particularly studied, the fetal blood sugar is lower than that of the mother. At birth the values in the kitten were somewhat higher than those of the mother. In one case in which an animal gave birth to four kittens during severe insulin hypoglycemia, the blood sugars in the latter were within the normal limits, but considerable increments were observed an hour after birth. The mother showed none of the usual hypoglycemic symptoms during parturition, although convulsions followed the same insulin dosage a few weeks later. Marked hyperglycemic reactions which were produced in the mother by emotional excitement, or by adrenalin or glucose administration, did

not affect notably the fetal glycemia. It is indicated that during the later stages of gestation, important adjustments are able to be carried out by the fetus in response to various emergency conditions that may be imposed on the mother.—Author's Summary.

Psychiatric reactions from dysinsulinism in a diabetic. Cronin, H. J., J. Nerv. & Ment. Dis. **74**: 478. 1931.

In the successful treatment of any organic disease the psycho-physical organism as a whole must be considered rather than the isolated treatment of the symptoms relating to one organ. In the case described there was a general constitutional inferiority with glandular, ophthalmic, neurologic and psychiatric symptoms. The patient was a student 22 years of age of the asthenic type who complained of mental confusion, examination anxiety, inability to concentrate, memory difficulties and physical weakness. She was over-conscientious, hypercritical, and unfriendly toward associates. At times of stress in college she developed eye symptoms which were unrelieved by refraction or treatment. Some months previous to examination she developed a series of skin infections that required surgical treatment. Concomitant with the skin infections, she was mentally confused, repeated words in a stereotyped manner and complained of insomnia. Physical examination revealed an old arrested tuberculosis, glycosurea 2½%; and blood sugar 200 mm. She was 24% underweight. Diabetic therapy was carried on with psychotherapy. When the patient increased her insulin or decreased her carbohydrates she had a return of the ophthalmic and psychiatric reactions. After one particular self-administered injection, she had an attack of mental excitement of four hours' duration in which diplopia was the first symptom. Then followed localized areas of anaesthesia, mental confusion, irrational behavior and assaultive attacks. After the height of the attack had lessened, she was elated and unrepressed. In this attack there was a reversal of her usual character traits with belligerency, aggressiveness and expression of repressed erotism. Following the attack she became again quiet and docile. As the patient was observed over a period of months there was some improvement in the diabetic condition but there was a gradual loss of effect toward the environment with listlessness and a slight degree of mental deterioration.—Author's Abst.

Clinical course of hyperinsulinemia. Fedoroff, P. A., Vrach. gaz. **35**: 585. 1931. Abst., J. A. M. A. **97**: 749.

Fedoroff analyzes the results of surgical intervention in cases of an entirely new entity named hyperinsulinemia. He states that to the Russian surgeon Oppel belongs the honor of giving the first comprehensive description of it and of performing an operation on a patient with a typical hyperinsulinemia. Oppel's surgical treatment was based on the assumption that among many other therapeutic measures in the treatment of hyperfunctioning of the endocrine glands should also be included resection of a part of the diseased organ. The symptoms of hyperinsulinemia are lowered blood pressure, hypoglycemia, increased tolerance of blood to sugar assimilation and obesity. In the author's opinion the disease is caused by hyperfunctioning of the islands of Langerhans. He states that severe forms of hyperinsulinemia often develop rapidly and even end fatally. He cites in most instances the observations of American investigators, who extensively used resection of a part of the gland in all similar cases. There are two conditions that may be encountered on the operating table: one may find a tumor of the insular apparatus or there will be no changes in it whatever. The author concludes by suggesting that surgical intervention be not delayed as it is the only means of saving the life of the patient; he recommends that at least an exploratory laparotomy be performed because it is not yet possible to make a preoperative diagnosis of a tumor of the pancreas.

Action of drugs on internal secretion of pancreas (Acción directa de diversos agentes sobre la secreción interna del páncreas). Foglia, V. G., Rev. Soc. argent. de biol. **7**: 361. 1931.

The internal secretion of the pancreas is not modified by injecting into the pancreatic artery of a vascular graft of the organ, the following substances: methylene blue, standard powder of posterior pituitary lobe, pilocarpin, ergotamin, aceticholin, nicotin.—J. S. Lewis.

Pancreatic diabetes in hypophysectomized dogs (Le diabéte pancréatique des chiens hypophysectomisés).

Diabetic conditions in dogs without hypophysis or pancreas (Les troubles diabétiques chez les chiens privés d'hypophyse et de pancréas). Houssay, B. A. and A. Biasotti, Compt. rend. Soc. de biol. **105**: 121; 124. 1930.

Nine dogs, which successfully survived the immediate effects of the two operations, lived without treatment for 25 to 160 days as against a maximum of 28 days for depancreatized dogs. There was some utilization of sugar by the doubly operated dogs. The glycemia and glycosurea was less intense.
—J. C. D.

Influenciation of a case of diabetes insipidus through corpus luteum extract (Beeinflussung eines Falles von Diabetes insipidus durch Corpus-luteum-Extrakt). Meyer-Nobel, K., München. med. Wchnschr. **77**: 1844. 1930.

Considerable improvement was noted in a patient with diabetes insipidus, who used to deteriorate during very intense menstruation, by the administration of "Luteoglandol."—W. Raab.

The influence of injections of sucrose and invert sugar upon ketonuria and ketonemia in diabetes mellitus (Invertzucker- und Rohrzuckerinjektionen bei Diabetes mellitus und ihr Einfluss auf den Ketonkörperspiegel). Pucsko, O., Deutsches Arch. f. klin. Med. **170**: 203. 1931. Abst., Chem. Absts. **25**: 4609.

Glucose and fructose exhibit their maximum antiketogenic action when they are injected as invert sugar; this mixture when injected alone has a favorable effect upon both sugar and ketonic content in diabetics, and the effect is heightened if the injection is followed by treatment with insulin. Saccharose alone exerts a very gradual influence upon ketone body concentration; when saccharose is accompanied by insulin the effect of the insulin is lessened or delayed.

The delayed variations in the glycogen of the liver and muscles in normal dogs after repeated doses of insulin (Les variations tardives du glycogène hépatique et musculaire chez la chien normal sous l'influence d'injections répétées d'insuline). Rathery, F., S. Gibert and Y. Laurent, Compt. rend. Soc. de biol. **104**: 652. 1930.

In four dogs there was a reduction of liver glycogen on the average and no constant change in the muscle.—J. C. D.

The late variations in liver and muscle glycogen in depancreatized dogs given repeated doses of insulin (Les variations tardives du glycogène hépatique et musculaire chez le chien dépancréaté sous l'influence d'injections répétées d'insuline). Rathery, F., S. Gibert and Y. Laurent, Compt. rend. Soc. de biol. **104**: 1224. 1930.

Five depancreatized dogs were given 30 units of insulin each day for 5 days and examined 17-19 hours after the last injection. When compared with uninjected depancreatized animals, there was no difference.—J. C. D.

Observations on the complex symptoms which accompany hypoglycemia (Beobachtungen über den hypoglykämischen Symptomenkomplex). Reinwein, H., Deutsche med. Wchnschr. **57**: 571. 1931.

A discussion of clinical symptoms which accompany hypoglycemia produced by overdosage of insulin is given. Seven cases are described, each illustrating a slightly different type and problem. In conclusion the author stresses the importance of being on the lookout for hypoglycemia in all stages of unconsciousness, unexpected hilarity, drowsiness, etc.—H. J. J.

Jerusalem artichokes and liver in the treatment of diabetes mellitus. Soskin, S., H. F. Binswanger and S. Strouse, Am. J. M. Sc. **182**: 675. 1931.

Five patients, on carefully controlled diets, were fed amounts of artichokes varying from 20-70 grams for 2-16 days. There was no evidence that

the artichokes, which consisted largely of ~~inulin~~ and ~~inulin~~-like substances, were of any value in the treatment of diabetes. Liver, 180 grams for 3-10 days, did not have any appreciable effect on diabetes as judged by the urinary sugar excretion.—E. L.

Diabetic pyorrhea. Williams, J. B., Am. J. M. Sc. **182**: 807. 1931.

The following dental symptoms were exhibited by untreated diabetics: Teeth were loose and gums hypertrophied, inflamed and ulcerated. The condition resembled pyorrhea. In treated diabetics, the teeth were firm and the mucous membrane, though soft and flabby, showed no signs of ulceration. Of the 138 diabetic patients, 135 either had pyorrhea or stated that they had had pyorrhea. The author believes that the modification of dental tissues induced by diabetes is so constant as to constitute a clinical entity and that there should be co-operation between the internist and the dentist in treatment.—E. L.

A study on the parathyroid enlargement in osteitis fibrosa generalisata. Ask-Upmark, E., Acta med.-Scandinav. **74**: 284. 1930.

A case report is given of a man aged 46 with generalized osteitis fibrosa who died five months after admission to the hospital. At autopsy only one parathyroid gland was found and this was enlarged to the size of a hazelnut. Bone changes typical of osteitis fibrosa were found. A single blood serum calcium determination was normal, 10.1 mgm. The author lists the 14 cases found in the literature in which removal of the parathyroids was done in cases of osteitis fibrosa generalisata. He considers that osteitis fibrosa generalisata is associated with and is possibly due to an enlargement of one or more of the parathyroid glands and this is primary to the bone disorders. He emphasizes the fact that in this disease there is a marked disturbance of the calcium metabolism. On the other hand, osteitis deformans Paget is not associated with an enlargement of the parathyroid glands and the blood calcium is normal. The author advises parathyroidectomy in cases of osteitis fibrosa, especially if these glands are enlarged, and at the same time he emphasizes the possibility of the occurrence of post operative tetany.—Irene Sandiford.

Failure of irradiated ergosterol to relieve parathyroid tetany. Findley, T., Jr., Ann. Int. Med. **4**: 1144. 1931.

A case of post-operative parathyroid tetany associated with epilepsy and acute psychosis is reported. In an effort to determine whether or not irradiated ergosterol, even in massive doses, would increase the absorption of calcium from the intestinal tract, the patient was stabilized by placing her upon a low calcium diet for two weeks. The average daily ration contained 0.1 gm. of calcium, 0.5 gm. of phosphorus, 2-3 gm. of NaCl, sufficient protein to maintain nitrogen equilibrium, and enough calories to prevent loss of weight. On this diet no significant changes occurred in the levels of blood calcium or phosphorus during this period. Ten grams of calcium gluconate were then administered orally on an empty stomach, and the effects on the serum calcium noted by hourly determinations for 6 hours after ingestion. The anticipated rise was obtained. Later, viosterol (Parke, Davis & Company, a preparation said to contain about 0.7 mgm. of irradiated ergosterol per cc.) was administered under the same conditions in daily doses of 20 cc. for two weeks, and the same calcium absorption test repeated. The two curves showed no differences which might be attributed to increased absorption from the intestinal tract.

—Author's Abst.

Parathyroid hypertrophy after denervation of the carotid sinus and the cardio aortic zone (Hyperthrophie parathyroïdienne après énervation des sinus carotidiens et de la zone cardio-aortique). Goormaghtigh, N. and C. Heymans, Compt. rend. Soc. de biol. **106**: 474. 1931.

In rabbits such an operation is followed by a marked enlargement of the external parathyroids and some enlargement of the internal. Cell multiplication as well as cell enlargement is evident.—J. C. D.

The diffusible calcium of the blood stream in tetany. Gunther, L. and D. M. Greenberg, Arch. Int. Med. **47**: 660. 1931.

A study has been made of the serum calcium distribution in cases of tetany of diverse origin. In the case of infantile tetany, tetany due to parathyroid deficiency and as a result of osteomalacia, the significant finding has been a reduction in the diffusible calcium fraction. On the other hand, in tetany induced by hyperventilation, the diffusible calcium remains unchanged In other conditions where muscular twitching and nervous irritability are marked symptoms, namely, certain muscle cramps, hysteria, petit mal and hyperthyroidism, no alterations were found in the diffusible or non-diffusible calcium. From the findings it is asserted that tetany cannot be ascribed to any single etiological factor, i.e., solely to either a reduction in calcium ion concentration or an alkaline shift in the bodily acid-base balance.

—D. M. Greenberg.

Calcium in relation to cataract I. In vitro. Kirby, D. B., Arch. f. Ophth. **5**: 856. 1931.

Of all the tissues of the body the crystalline lens seems best adapted to valid experiments in vitro because of the peculiar conditions surrounding it in vivo. It does not depend on direct circulation of blood but on the aqueous humor for its metabolism. It should be possible to produce a true and complete synthetic aqueous humor and, simulating the other conditions, to cause the entire lens to live in vitro and to maintain its transparency. Experiments were performed with living lens epithelial cells to determine the effect of increasing or decreasing the calcium content of the experimental medium. The amount of calcium in the control medium was subject to variations, owing to the fluctuations in the calcium content of the chick embryo extract and of the chicken plasma. It was found that epithelial cells of the lens in vitro will withstand relatively large increases in the calcium content of the experimental medium over the level for the control medium without showing any great difference in microscopic appearance, growth or activity. It was only when the medium contained such a large increase that precipitations of calcium compounds occurred that the medium became toxic to the cells. On the other hand, relatively slight reductions of the calcium content of the medium produced toxic reactions in the cells. The fraction of the calcium that was reduced in the experimental medium was the ionized diffusible portion, as the calcium in Tyrode's solution is in that form. The normal aqueous humor probably contains only ionized and nonionized diffusible calcium. The humors of the body and of the eye have a variable calcium content and the ratio of the calcium to the potassium content varies for different humors. Again, the humors differ tremendously from the cells and tissues. An interesting parallel was found between the calcium and potassium ratio of the red blood corpuscles and the crystalline lens as compared with that of the blood serum, aqueous, spinal fluid and various fluids used in physiologic experiments. In cataract, the ratio is in part reversed.—Author's Abst.

Calcium in relation to cataract II. In vitro. Kirby, D. B., Arch. f. Ophth. **5**: 868. 1931.

The study of the relation of calcium to cataract was undertaken to clarify the situation in regard to this subject. It was desired: (1) to assemble the latest information regarding calcium metabolism in general; (2) to know the importance of calcium in the normal growth and metabolism of the crystalline lens; (3) to learn the cause and prevention of tetany cataract in both infants and adults; (4) to find the reason for the deposition of calcium in senile cataract; (5) to discover whether patients with senile cataract suffered from calcium deficiency or excess, and (6) to know whether the administration of calcium or parathyroid extract was indicated in cases of senile cataract. The calcium in the aqueous represents the ionized and nonionized diffusible fraction from the total calcium of the blood plasma. There is an extremely small amount present normally in the crystalline lens, but the importance of the element in combination with the other elements is out of all proportion to the chemicals involved. Calcium is greatly increased in the lens in senile cataract. Calcium deficiency in cases of infantile tetany is undoubtedly responsible for the development of cataract in these cases. Even though the factors that produce and cure rickets are the same as those for tetany, there is some differ-

ence that has not as yet been discovered between rickets and tetany, and cataract is linked up with the tetany rather than with the rickets complex. No case of tetany cataract has been seen at the Babies' Hospital in the past two years. The widespread knowledge and use of the factors preventing and controlling rickets and tetany have led to a decrease in the number of tetany cataracts. One illustrative case of postoperative tetany with cataracts from the 38 cases to be found in the literature is reviewed. The important points to be learned are: (1) prevention of the removal of parathyroid tissue at the time of thyroidectomy, (2) early treatment of such patients as show parathyroid deficiency. A great many of the latter cases are undoubtedly only temporary, due to vascular disturbances. The pathogenesis of tetany cataract implies a reduction in the serum, aqueous and lens calcium content with electrochemical changes and disturbance of equilibrium of the inorganic elements in the lens causing changes in the labile colloidal solution of the lens protein. Once these changes are established, the administration of calcium or parathyroid extract does not cause a restoration of the normal state of the protein. Not all tetany cataracts progress to complete opacity. The prognosis in complete tetany cataract depends on the operative removal of the cataract. In cases of senile cataract, the deposition of calcium most probably results from (1) very slow death of lens tissue dependent on nutritional deficiency; (2) degeneration of the lens protein with lipoid by-products; (3) local concentration of calcium by absorption to the large molecules of the lipoids, and (4) deposition of this calcium by a change in the pH toward the alkaline side. There was no evidence of tetany or latent tetany in a series of cases of senile cataract. Two separate series of cases of senile cataract were investigated as to the serum calcium level. In the first series 28 men, aged from 52 to 80, had an average level of 11.3 mgm. per hundred cubic centimeters, while 25 women, aged from 52 to 82, had an average level of 10.9 mgm. The second series included 33 men, from 45 to 82 years of age, whose average serum calcium level was 10.29 mgm., and 50 women, aged from 50 to 82, whose level was 10.34 mgm. No variation could be found according to age, sex, type of cataract, visual quotient or complicating ocular or general disease. There is therefore no evidence of calcium deficiency as far as the blood serum values are concerned in cases of senile cataract. In the study of the endogenous calcium metabolism in cases of senile cataract, the relation of the intake of calcium in the diet was carefully calculated and compared with the output of calcium in the urine and feces. The results showed that the patients were in perfect or slightly positive balance when on a neutral or slightly alkaline diet, but when on an acid residue diet or when receiving injections of parathyroid extract, they were in negative balance, excreting more calcium than they ingested. In other words, these patients were responding normally to the factors influencing calcium metabolism and were utilizing their calcium properly. There was no indication for the administration of calcium salts to any of these patients. If patients with senile cataract are found to have normal serum calcium but are in negative calcium balance, it is better to correct the factor that is producing the latter than to administer calcium salts to them to make up the deficiency. There was no reason for the administration of parathyroid extract to these patients, as they had sufficient serum calcium. Parathyroid extract-Collip produced excess urinary excretion of calcium, but the excess calcium that was mobilized from the tissues undoubtedly came from the normal storehouse, the bony trabeculae, where it is easily available, and not from the deposits in the cataracts.—Author's Abst.

Effect of parathyroid extract on tonus and peristalsis in the stomach and intestine (Zur Wirkung des Epithelkörperchenextraktes auf Tonus und Peristaltik des Magens). Mahler, P. and A. Beutel, Endokrinologie, **9**: 17. 1931.

The authors noted, in the treatment of patients who required parathyroid extract, that some individuals incidentally were relieved from long-standing spastic digestive trouble without known organic cause. They therefore studied the effects of this extract upon the tone and peristaltic activity of stomach and intestine in patients receiving such treatment; both roentgenoscopy and the balloon-method were used. They conclude that in most people parathyroid extract has no noteworthy effect on gastrointestinal peristalsis; a few cases treated for several days showed an accelerated emptying of the stomach. In most cases, however, the gastrointestinal tonus was lowered and the tracings showed flattening. The relevant literature is reviewed.—F. T. Jung.

Osseous diseases and the parathyroids (Maladies osseuses et parathyroïdes). Snapper, I., Ann. de méd. **29**: 201. 1931.

A detailed description is given of a severe case of osteitis fibrosa (von Recklinghausen) in which removal of a parathyroid adenoma was followed by re-calcification of the skeleton and symptomatic improvement which practically amounted to a cure. In this and other cases reported in the recent literature, a negative calcium and phosphorus balance has been indicated by excessive urinary excretion of calcium and phosphorus. The serum calcium has been high and the serum phosphorus below normal, conditions exactly opposite to those found in parathyroid insufficiency. The pathogenesis of this disease is thus clearly based on parathyroid overfunction. Biochemical examination of eight cases of osteitis deformans (Paget's disease) and one of Leontiasis ossea revealed normal serum calcium and serum phosphorus and normal urinary excretion of calcium and phosphorus in all. The operative recovery of normal appearing parathyroid glands from two of these cases was without influence on the course of the disease. While many pathologists, basing their opinions on anatomical features, consider that the skeletal disease of von Recklinghausen and that of Paget's are intimately related, it is evident that striking differences exist clinically, biochemically and in their respective pathogenesis.
—R. M. Wilder.

A study of the action of irradiated ergosterol, and of its relationship to parathyroid function. Taylor, N. B., C. B. Weld, H. D. Branion and H. D. Kay, Canad. M. A. J. **25**: 20. 1931.

This paper gives a condensed account of a number of experiments from which fresh evidence has been derived for a close relationship between the overdosage effects of irradiated ergosterol and parathyroid function. The relationship is thought to be most probably a direct one, namely, the stimulation of parathyroid tissue by the sterol. Comparing the effects of large doses of irradiated ergosterol and of parathormone, many similarities are found. (1) Effect on the course of tetany. Rapid and complete cure by a single dose of irradiated ergosterol (1 cc. of 10,000 D) or of parathormone (20 units). This applies to dogs which have had the simple thyroparathyroidectomy performed. Those which in addition have had a free dissection of the neck for removal of any accessory parathyroid tissue surgically accessible, develop a tetany which is very refractory to treatment with irradiated ergosterol. (2) The psychic changes, lassitude, anorexia, vomiting, loss of weight, weakness, the passage of blood in the stools and vomitus, and other symptoms are identical in the two conditions when the acute type of poisoning is induced by large doses. With maximal doses the duration of life is about 24 hours longer with irradiated ergosterol. (3) Post mortem. The macroscopic and histological findings are identical. The most prominent features are hemorrhages into lung alveolar walls, stomach and small intestine mucosa and lumen, and bone marrow. (4) Blood changes. Hypercalcemia, rise in N.P.N., late rise in inorganic phosphate and terminal fall in calcium occur at the same time and are of the same magnitude in both conditions. Plasma phosphatase is reduced. (5) Excretion of calcium and phosphorus. So far as data are available, both agents affect these elements similarly. (6) Source of the excess calcium. From within the body in both conditions, and most probably from the bones. (7) Urinary changes. Both substances affect the volume, titrable acidity, phosphorus and calcium in the same way. (8) Species susceptibility. Those species resistant to parathormone overdosage are also resistant, to about the same degree, to overdosage with irradiated ergosterol. The dog and the human subject are relatively highly susceptible to the hormone, and the dog to the sterol. Hence the human may be susceptible to large doses of irradiated ergosterol; clinical observations are cited as direct evidence of this. On the other hand, the therapeutic dose of the sterol is of the same order of magnitude for all the species examined. (9) Calcium deposition in the soft tissues. Metastatic calcification results from the prolonged administration of either substance. These experiments and those of the literature indicate that upon increasing the dosage of irradiated ergosterol from small to very large amounts, its effect upon calcium metabolism becomes reversed, a parathormone-like action becoming manifest. The precise level at which the reversal of action occurs is unknown. Much larger doses of the sterol can be tolerated subcutaneously or by inunction, than intravenously or by mouth. The rat lethal dose per gram body weight is 500-1000 times that for a dog.—C. B. Weld.

The relations between Hassalls corpuscles and the blood vessels in the thymus of the human foetus (Sur le rapport entre les corpuscles de Hassall et les vaisseaux sanguins voisins, dans le thymus des foetus humains). Kostowiecki, M., Compt. rend. Soc. de biol. **105**: 417. 1930.

The thymus was followed from three months to birth. The corpuscles arose in two ways, from hypertrophy of reticular cells independent of blood vessels and from the degeneration of capillaries or small veins. In the latter case the endothelium and vessel wall degenerated while the reticular tissue surrounding it hypertrophied to form the bulk of the corpuscle.—J. C. D.

Experimental research on the action of thymus extirpation upon goiter production (Experimentelle Untersuchung über die Einwirkung der Thymusexstirpation auf die Kropferzeugung). Stahnke, E., Deutsche. Ztschr. f. Chir. **224**: 129. 1930. Abst., Biol. Absts. **5**: 1961.

The disputed question whether thymectomy promotes or hinders goiter or has no effect on it was studied on 16 litters or about 81 young rats in all. They were fed Tanabe's goiter-producing diet (barley, beef and endive, and a saturated solution of $CaCl_2$ in distilled water). In the second week of life all but one control in each litter were thymectomized. Necropsy not later than 180 days afterward showed a diffuse colloid struma in the operated animals instead of the Basedow-like structure present in the non-operated animals.

Pathology of the thyroid gland of the human fetus and the new born infant. Abbott, A. C. and R. P. Ball, Canad. M. A. J. **24**: 347. 1931.

In the gross and microscopic examination of 100 human thyroid glands of the new-born fetus 41% showed anatomical evidence of disease. This was based upon the study of material from supposedly pathological organisms, the incidence in the products of normal consecutive deliveries might be at great variance from the above.—A. T. C.

Changes according to age in the thyroid in mammals (Evolution de la thryroïde en fonction de l'âge chez les mammifères). Aron, M., Compt. rend. Soc. de biol. **105**: 581. 1930.

This is a brief account of the growth of the gland from birth to three weeks in guinea pigs. Two graphs show that its growth is not directly proportional to age or weight.—J. C. D.

Effect of removal of the cervical sympathetic on thyroid function (Influence de l'ablation du sympathique cervical sur le fonctionnement thyroïdien). Aron, M. and W. Dobrzaniecki, Compt. rend. Soc. de biol. **104**: 1323. 1930.

Injections of extract of the anterior lobe of the hypophysis produce normally intense activity in the thyroid. In seven rabbits after removal of the cervical sympathetic from the superior to the stellate ganglion on both sides, injections of active hypophyseal extract failed to stimulate the thyroid. When only the superior cervical ganglion was removed the extract was effective shortly after the operation but ineffective if given a month later.—J. C. D.

An original method of estimating the thyrotoxic states. Bartlett, W. and W. Bartlett, Jr., South. M. J. **25**: 12. 1932.

The test reported is based on the thyrotoxic patient's outstanding physiologic defect, sensitiveness to oxygen deficiency. A preliminary report of detailed observations at intervals before and after operation in 35 cases showed that the duration of voluntary apnea could be correlated with characteristic changes in pulse rate, blood pressure, and basal metabolism. The ability to hold the breath is measured in seconds after (a) deep inspiration and, following a period of rest, (b) after deep expiration. The two figures are expressed as a fraction in which the former represents the numerator and the latter the denominator. It has been found that the numerator (inspiratory phase) varies primarily with changes in circulation, and that the denominator (expiratory phase) varies primarily with gross changes in basal metabolism. This differential response of the two phases must be considered in following

and interpreting changes in the patient's condition. Besides changes in duration of the two phases, the ratio between them varies and is of value as an indication for subtotal or for stage operations. The ratio in health is approximately 2:1. Acute, untreated thyrotoxic patients fall into two groups, those without past athletic training or physical work giving a ratio approaching 1:1; those who have had such training are more apt to show higher ratios (3:1 or 4:1). As both groups approach operability, the ratios return toward the normal of 2:1. Expected normal duration of the two phases varies with the individual; discussion of normal values, of factors affecting them, of clinical interpretation of the test and its technique are to be found both in the preliminary report and in this general presentation of it. The test is regarded as being the most generally useful and completely reliable.—Authors' Abst.

Clinical anatomical biological parallels in Basedow's disease (Klinisch-Anatomische Biologische Paralelen bei Morbus Basedowi). Berliand, N., I. Rywkin and P. Ssacharoff, J. Medico-Biologique, **3**: 149. 1930.

The authors tried to determine if there is any connection between the anatomical structure of the thyroid gland in Basedow's disease and its biological activity. They also sought for a parallel between these two factors and the clinical course of the illness. To determine the biological activity of the thyroid taken from Basedow patients a small measured piece of this gland was given to axolotls. The metamorphosing action was then examined. Twenty glands were examined and 94 axolotls were used. All the glands were histologically examined. The Basedow patients were divided according to the clinical course of the disease before the operation into 3 groups: severe, medium and light. The thyroids removed from Basedow patients show varied biological activity upon axolotls according to their different structure. Parenchymatous thyroids have a smaller effect than colloidal ones. Thyroids rich in colloid have a stronger action than the glands with less colloid. The general histological changes which are characteristic in Basedow patients show no essential changes in their biological activity. The optimum dose which causes a quick and certain action in axolotls of 6-12 grams weight is between 0.2 and 0.4 gm. One case of thyroid from a Basedow patient was inactive. The authors could not establish a biological clinical parallel.—J. Gagnon.

Thyroxin and the specific dynamic action of sugar (Thyroxine et action spécifico-dynamique des hydrates de carbone). Coelho, E., Compt. rend. Soc. de biol. **105**: 143. 1930.

The subjects were given 100 grams of levulose and studied. Then for several days 12 mgm. of thyroxin were given by mouth or 4 mgm. subcutaneously. The subjects were again tested after levulose. In the thyroxin-treated cases the respiratory quotient was reduced to 0.93 as compared with 1.10 and the metabolic rate raised to 1500 as compared with 1200. The readings were taken an hour after the levulose meal. Thyroxin then has a definite action on the metabolism of carbohydrates which is opposed to that of insulin.—J. C. D.

Effect of stimulation of the cervical sympathetic on thyroid function (Influence de l'excitation du sympathique cervical sur le fonctionnement thyroïdien). Dobrzaniecki, W. and M. Aron, Compt. rend. Soc. de biol. **104**: 1321. 1930.

In 17 rabbits the cervical sympathetic was stimulated electrically at various points between the superior and the stellate ganglion. The lobe of the thyroid opposite the side to be stimulated was removed at the start of the experiment. The lobe on the side stimulated was taken out either immediately or from 5 to 24 hours later. Careful histological comparison failed to reveal any difference between the stimulated and non-stimulated sides.
—J. C. D.

Cytological studies on the guinea pig thyroid (Recherches caryométriques sur la glande thyroïde du cobaye). Florentin, P. and M. Grujic, Compt. rend. Soc. de biol. **105**: 938. 1930.

The thyroid in addition to follicular cells contains interfollicular cell masses. If the nuclei of the interfollicular cells are measured they show the grouping into definite sizes which is characteristic of tissues undergoing active division. This confirms the author's view that these interfollicular cell masses are embryonic and not senile thyroid cells.—J. C. D.

Effect of synthetic thyroxine on the urinary carbon and nitrogen (Action de l'injection de throxine synthétique sur la carbonurie et sur l'azoturie).

Effect of thyroidectomy alone and associated with injections of thyroxin on the urinary carbon and nitrogen (Action de la thyroïdectomie seule et accompagnée d'injections de thyroxine sur la carbonurie et sur l'azoturie). Fontès, G. and L. Thivolle, Compt. rend. Soc. de biol. **105**: 558; 559. 1930.

Two dogs received subcutaneous daily injections of 1 mgm. of thyroxin for two weeks. In another experiment the dosage was 2 mgm. In both series elimination of carbonates and nitrogen was increased independently of the dosage. The C/N ratio and the amount of urine were unchanged. Thyroidectomized dogs show a 25% increase in elimination of nitrogen with no change in carbonates. In these dogs injections of thyroxin increased the elimination of both substances but did not restore the C/N balance.—J. C. D.

The feather germ as indicator for thyroid preparations. Juhn, Mary and B. O. Barnes, Am. J. Physiol. **98**: 463. 1931.

Administration of thyroxin and thyreoglobulin causes the deposition of dark pigment granules in the formative region of the orange saddle feathers of Brown Leghorn capons and cocks. This reaction has been developed as an indicator for thyroid preparations: saddle feathers are plucked and regeneration allowed to proceed for about twenty days, then a single dose of thyroxin or thyreoglobulin is administered. Feather germ preparations made on successive days by splitting the feather germ longitudinally after plucking, record the first appearance and the time of persistence of the response in the pigmented sections proliferated daily from the papilla. The feather germ shows an increase in threshold or thyroxin from center to margin (i.e., from the shaft to the periphery of the vane of the definitive feather). Low doses record therefore at the center only and increasingly higher concentrations cause the formation of progressively wider pigmented zones. A positive response has been obtained with 0.5 mgm. thyroxin; the test is negative with inorganic iodine and the number of organic iodides and tissue extracts tested.
—Authors' Abst.

Contribution to the study of the etiology of goiter (Contribution a l'étude de l'étiologie du goitre). Lautier, R., Compt. rend. Soc. de biol. **105**: 23. 1930.

In 1928 Houda reported the isolation of a micro-organism from goiter cases. In two cases the writer has isolated by means of Houda's technic a similar organism and tentatively identified it as the diplo-strepto-bacillus of rheumatism.—J. C. D.

The action of synthetic thyroxin on the chronaxie of "gastrocnemiussciatic" preparations of Rana temporaria (Action de la thyroxine synthétique sur la chronaxie des préparations "Sciatique-Gastrocnémien" de Rana temporaria). Le Grand, A. and S. Ramos, Compt. rend. Soc. de biol. **104**: 1302. 1930.

Frogs were prepared and 1 mgm. of the synthetic thyroxin injected into the dorsal lymph sac. In 80% of the experiments there was a marked and prolonged reduction of chronaxie.—J. C. D.

Thyroxin, fat and lipoid metabolism (Thyroxin, Fett- und Lipoidstoffwechsel). Leites, S., Biochem. Ztschr. **22**: 101. 1930.

The effect of thyroxin on the alimentary lipemia of dogs was studied. The neutral fat content of the blood was determined by Bang's method, ketone bodies by Engfeldt-Pincussen's, cholesterol by Engelhardt-Smirnova's method. Thirty experiments were made on six dogs. Thyroxin (0.4 to 1.0 mgm) was injected subcutaneously immediately after ingestion of the fat meal, consisting of 100 cc. olive oil. It was found that thyroxin decreases alimentary lipemia and ketonemia. This effect of thyroxin is more pronounced in male than in female dogs. Previous castration weakens this effect of thyroxin in male dogs, increases it in female dogs. It is concluded that the male gonads "activate" the effect of thyroxin on fat transport, and the female gonads inactivate the same.—H. R. Rony.

Effect of certain therapeutic measures on the protein equilibrium of the thyroid (Action de certaines thérapeutiques sur l'équilibre protéique des thyroïdiens). Loeper, M., A. Lemaire and J. Tonnet, Compt. rend. Soc. de biol. **104**: 1201. 1930.

In hyperthyroidism the total blood albumin and the globulin are decreased. Administration of sodium borate, or tincture of iodine, as well as radiotherapy, or partial thyroidectomy, is followed by an increase of albumin and globulin. Their return to normal roughly parallels the effectiveness of the treatment. —J. C. D.

The influence of the thyroid gland upon the poisonous action of various drugs (Ueber den Einfluss der Schilddrüse auf die Giftwirkungen verschiedener Pharmaka). Miyake, T., Folia Endocrinol. Japon. **7**: 43. 1931.

The author investigated the resistance of white mice to morphine chloral hydrate, amylene hydrate, sodium veronal (barbital), ethylurethan, strychnine, hydroquinon, both with the addition of thyroid material and after extirpation of the gland with the following results: (1) The resistance of the mice to morphine is decreased by the addition of thyroid substance, but it is increased by thyroidectomy. (2) Thyroidectomized mice show a greater sensitivity to the narcotics of the alipathic series, especially to chloral hydrate, amylene hydrate, barbital and ethylurethan animals treated with thyroid material show less sensitivity to these drugs than normal animals. (3) The resistance of mice to strychnine and caffeine sodio-benzoate is lessened by addition of thyroid material. Also in rabbits the addition of thyroid material causes an increase in the sensitivity of caffeine sodio-benzoate. (4) The resistance of mice to veratrin is increased by thyroidectomy. Although the influence of the thyroid gland upon the poisonous action of arsenious acid is not especially marked the resistance of the mice to quinine is increased by addition of thyroid and lessened by thyroid extirpation. Thyroidectomized mice are more sensitive to colchicin and hydroquinon than normal animals.—J. Gagnon.

Dietetic treatment of hyperthyreosis. Moller, K. O., Hospitalstid. **74**: 124. 1931. Abst., J. A. M. A. **96**: 2006.

Moller found that the effect of experimental hyperthyreosis in rats was particularly well counteracted by a diet rich in fat and albumin, containing large quantities of vitamins, especially vitamins A and B, together with the necessary salts, and with the addition of calcium lactate. Muscle protein has an injurious effect and must be avoided.

On the pathogenesis of exophthalmic goiter. Decrease in elimination or in destruction of thyroxin? Vogt-Möller, P., Acta med. Scandinav. **76**: 437. 1931.

After a review of previous investigations on the Reid-Hunt reaction, this paper gives the results of experiments with tyrosine, tyramine, diiodotyrosine, pituitary and testicular optones. With the technique employed, these substances did not alter the outcome of the reaction. A report is made of positive reactions obtained with sera from patients suffering from hyperthyroid constitutions, with sera from patients with exophthalmic goiter and patients with advanced nephritis; also a positive reaction with serum from a normal individual, from whom the blood was taken immediately after (but not a short time after) an intravenous injection of thyroxin; further, a positive reaction with serum from a myxedematous patient after administration of very large amounts of thyroidin (more than required for normal metabolism). Mention is further made of negative reactions with sera from normal individuals and from patients with various diseases, and from a normal individual after administration of potassium iodide. On the basis of these investigations the following hypothesis is advanced as to the pathogenesis of exophthalmic goiter. In disposed individuals (hyperthyroid constitution) an additional thyroid hyperfunction is brought about by the well-known causes of exophthalmic goiter (to which may perhaps be added faulty diet), or it develops without such causal connection. The increased hormone content of the blood produces, through the sympathetic nervous system, an impairment of the partial function of the kidney, impeding to a greater or smaller extent the elimination of thyroxin (or closely related substances), so that the accumulation of these substances in

the organism is further increased (eventually, degenerative processes may develop in the kidney epithelium). Possibly the precipitating cause of hyperthyroidism (toxins, etc.) may also have a direct effect upon the kidney—besides the indirect effect through the thyroid—and thus contribute to the development of the symptom complex, exophthalmic goiter. Or it may possibly be connected with a change (decrease) in the destruction of thyroxin. It is pointed out that the so-called hyperfunction and hypofunction of the endocrine organs are also explainable as results of changes in the destruction or elimination of the respective hormone.—Author's Summary.

Hyperthyroidism; a statistical presentation of its symptomatology. Wallace, H. L., Edinburgh M. J. **38**: 578. 1931.

This is a study of 452 female and 58 male patients from 10 to 65 years of age. Table and graphs show the frequency of the major symptoms, etc. The results confirm the usually accepted picture of the disease.—J. C. D.

The production of hyperplasia of the thyroid gland by chemical means, with special reference to purine bases and their derivatives. Cole, W. H., N. A. Womack and W. H. Ellett, Arch. Surg. **22**: 926. 1931.

In attempting to find a possible chemical explanation for the production of the hyperplasia, desquamation, loss of colloid and decrease in iodine content in the thyroid gland, by certain infections and toxemias as observed by ourselves and others, we encountered various noteworthy facts. On certain occasions, these changes were produced to a marked degree by certain drugs, including especially caffeine, theophylline, xanthine and histamine when given in lethal or sublethal doses. The fact that the above mentioned changes were produced by this group of chemicals and not at all by the inorganic drugs used, suggests that by-products of protein catabolism might be important factors in the production of the pathological changes in the thyroid as produced experimentally by infections and toxemias. Most of the changes do not occur until the animal shows severe symptoms from the drug. To obviate possibility of post mortem change, sections of the thyroid must be removed at death or a few minutes after death. It is difficult to explain why on numerous occasions no changes in the thyroid were produced. Since we had noted in previous work that iodine would protect the thyroid of animals from the pathological changes mentioned above, we have assumed that the intake of excessive amounts of iodine in the animal's food might be the factor in the prevention of production of pathological changes. It is, of course, possible that there are other unknown physiological factors which make the thyroid more resistant in some instances than others.—W. H. Cole.

Hyperthyroidism associated with Parkinsonian syndrome. Wechsler, I. S. and N. Savitsky, J. A. M. A. **97**: 1283. 1931. Abst., A. M. A.

The authors note that the association of exophthalmic goiter with paralysis agitans is comparatively rare. Most of the cases reported in the literature show that the association is an accidental one. In the majority of instances the hyperthyroidism preceded the onset of the parkinsonian syndrome. In recent years, attention has been called to the presence of signs and symptoms referable to the vegetative nervous system in acute and in chronic encephalitis, which have a predilection for the basal ganglion-midbrain regions. But even before the involvement of the hypothalamic vegetative centers was recognized as the cause of metabolic and other disturbances, the sympathetic system was believed to be affected in exophthalmic goiter and to bear some relation to it. More recently, the suprarenals, the medulla of which is of the chromaffin sympathetic system, have been shown to stand in definite causal relation to hyperthyroidism. From time to time, suggestions have been made that physiologic or pathologic disturbances in the vegetative centers of the interbrain may have something to do with the production of many syndromes previously regarded as independent disease entities. The question, too, has been raised whether, in a syndrome such as hepatolenticular degeneration, the disease of the liver causes the changes in the brain, or, conversely, the involvement of the striatum leads to secondary disturbances in the liver. In encephalitis it has long been known that what may be regarded as dysthyroid symptoms were frequently a part of the clinical picture, even though there was no true exophthalmic goiter.

The speculation is also justified as to whether the tremor of hyperthyroidism is not in effect the result of secondary changes in the striatum. In view of all this, the question now arises whether exophthalmic goiter may not in some way be the result of some altered physiologic state or pathologic change of the hypothalamic vegetative centers. The proximity of these structures to the regions affected in paralysis agitans and the occurrence of hyperthyroidism with parkinsonism in two cases reported by the authors in which the one syndrome preceded the other may possibly furnish clinical confirmation of theoretical views. In any event the cases, aside from their speculative interest, are worthy of record because of their clinical rarity. Of clinical interest in both the cases was the difficulty in dissociating the hyperthyroid from the parkinsonian tremor. The former is much finer and more rapid, but it overlaid the coarser and slower oscillations of basal ganglion origin. The improvement following thyroidectomy subtracted, as it were, the overtone of tremor and improved the underlying basal ganglion syndrome to some extent. But it may well be that the thyroidal tremor is in reality of basal ganglion origin and caused by toxic changes in those structures. It is interesting, too, that the surgeons hesitated to operate, and it was only after urging by the neurologist and assurance that the paralysis agitans in itself was no contraindication that operation was performed.